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Original Articles

Rupture of the Spleen: A Complication of Erythroblastosis Fetalis 159
Herbert F. Philipsborn, Jr., Howard S. Traisman and David Greer, Jr.

Cerebral Thrombosis in Young Adults . . . 162
Louis Berlin, Bernard Tumarkin and Herbert L. Martin

Nonbacterial Regional Lymphadenitis ("Cat-Scratch Fever"): An Evaluation of the Diagnostic Intradermal Test 166
Joseph J. McGovern, Lawrence J. Kunz and Frederic M. Blodgett

A Comparison of the Efficacy of Tetracycline and Penicillin in the Treatment of Pneumococcal Pneumonia 173
E. Frei, III, C. R. Auner, T. E. Van Metre, Jr., and C. G. Zubrod

Massachusetts Medical Society 199
Massachusetts Department of Public Health Notices 199

Medical Progress

Clinical Pulmonary Physiology (To be continued) 177
Edward A. Gaensler

Medical Intelligence

Prolonged Staphylococcemia: Report of a Case 185
Harold C. Blog, Charles A. R. Connor, Walter Newman and Michael Kenney

Doctors Afield: Alexander Borodin 187
A. K. Garland

Case Records of the Massachusetts General Hospital . . 189

Editorials

Children's Hospital Honored 197
Dr. Faulkner Called to M. I. T. 197
Interim Session 198
Lantern-Slide Project for Case Records . . . 198

Correspondence 200
Books Received 200

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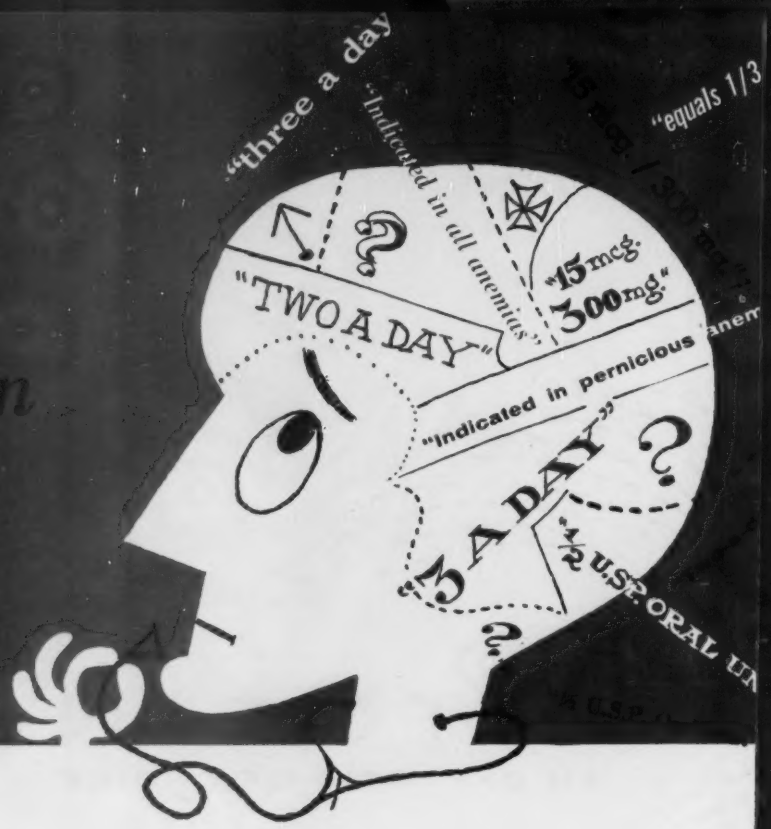

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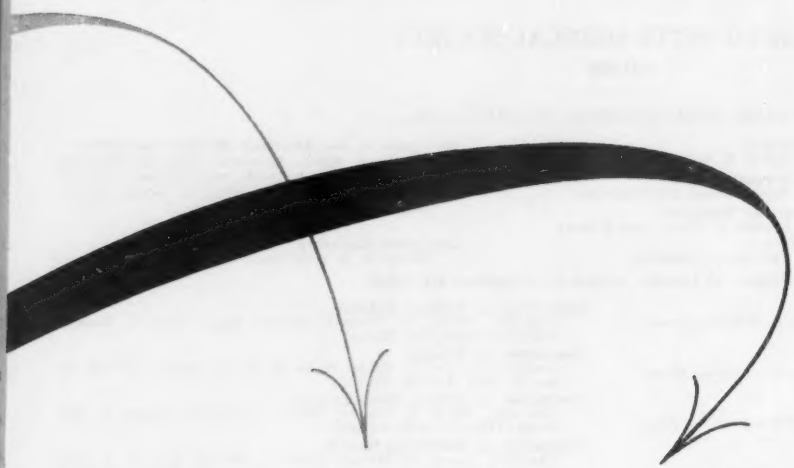

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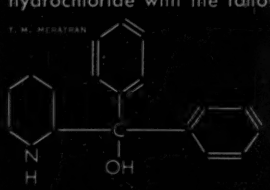

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1. Heath, R. C.: Discussion of paper by Howard D. Fabing (alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant in the treatment of blepharospasm, spasmodic torticollis and narcolepsy) presented before the American Neurological Association, Atlantic City, June 14, 1954. 2. Fabing, H. D., Hawkins, J. R., Moulton, J. A. L.: Clinical studies on alpha-(2-piperidyl) benzhydrol hydrochloride, a new antidepressant drug. Presented before the American Psychiatric Association, St. Louis, Missouri, May 3, 1954. 3. Fabing, H. D.: Alpha-(2-piperidyl) benzhydrol hydrochloride, a new central stimulant, in the treatment of blepharospasm, spasmodic torticollis and narcolepsy; preliminary report (Motion Picture Demonstration), American Neurological Association, June 14, 1954. 4. Himwich, H. E.: Discussion of paper (reference 2), American Psychiatric Association, May 3, 1954.

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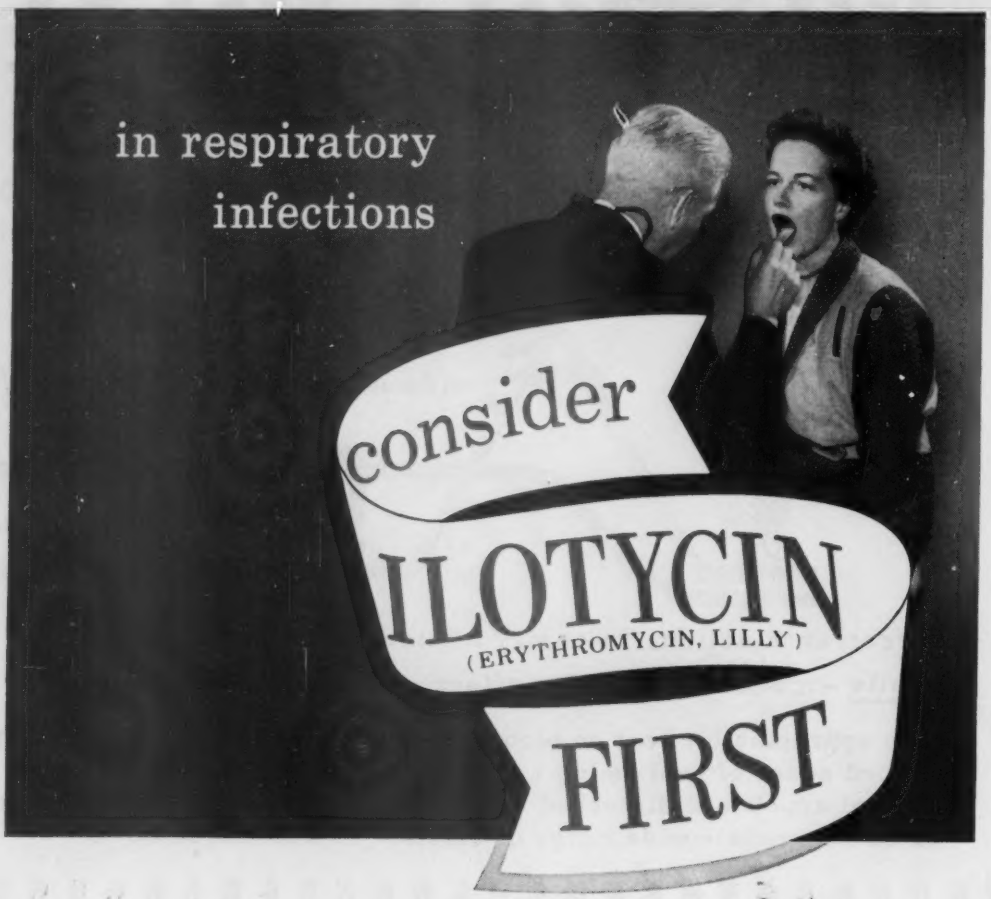

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RUPTURE OF THE SPLEEN*

A Complication of Erythroblastosis Fetalis

HERBERT F. PHILIPSBORN, JR., M.D.,† HOWARD S. TRAISMAN, M.D.,† AND DAVID GREER, JR., M.D.‡

CHICAGO

THE purpose of this paper is to discuss 4 cases of erythroblastosis fetalis complicated by rupture of the spleen. In 3 infants exchange transfusion had been completed. In the other death occurred before definitive therapy. In each case splenic rupture was discovered at autopsy.

The infrequency of this complication is established by the fact that a review of the literature yielded the report of only 1 such case, that of Slotkowski and Hand[1] in 1948. This is the first of the 4 cases to which we refer. In the same year Gruenwald[2] mentioned a case in which rupture of the spleen was discovered at autopsy; however, in this patient the primary diagnosis of erythroblastosis fetalis was not established. Diamond[3] has stated that he can recall only 1 case of rupture of the spleen among the erythroblastotic infants for whom he has cared; knee-to-forehead flexion was used as a means of postnatal resuscitation. Scott and Bowman,[4] reviewing cases of ruptured spleen in childhood, reported no case of splenic rupture occurring in an erythroblastotic infant. Mollison[5] has seen over 300 infants with hemolytic disease of the newborn, and has never suspected splenic rupture clinically, nor has he seen it at autopsy.

CASE REPORTS

CASE 1.¶ M., a male infant, was admitted to the hospital at 16 hours of age. He was lethargic and icteric, and weighed 7 pounds, 7 ounces at birth. The hemoglobin was 4.5 gm. per 100 cc., and the red-cell count 1,240,000 at 12 hours of age. The blood was Type O, Rh positive. The mother was para III, gravida II, having delivered twins 2 years previously, 1 of whom had died of "a knot in the umbilical cord." The viable twin became jaundiced on the 2d day of life, but no transfusion was given. The mother was Type O, Rh negative, and the father was Type O, Rh positive.

Physical examination showed an icteric, lethargic infant with generalized petechiae. The temperature was 96.1°F. Respirations were poor, and the heart sounds were distant. The liver extended to the umbilicus, and the spleen to the iliac crest.

An exchange transfusion was started. Midway through the procedure, the patient suddenly died. Calcium gluconate had been administered, and 0.2 cc. of heparin (200 units) had been injected into the radial artery at the start of the procedure.

The pertinent findings at autopsy were limited to the spleen. A clot was found in the left upper quadrant covering the undersurface of the spleen and neighboring viscera. The spleen weighed 42 gm. (normal weight, 8 gm.), and the capsule was absent from its renal surface. There was no evidence of tearing into the parenchyma.

Microscopical examination was negative except for the liver and spleen. The liver contained many foci of extramedullary hematopoiesis with large, localized masses of immature cells in the sinusoidal spaces. The splenic capsule and trabeculae were thinned. The lymph follicles were greatly reduced in size; the germinal centers were absent, and many immature red cells were present in the parenchyma. The capsule was elevated from the underlying parenchyma in sections from the hilus.

CASE 2. B.H., a 12-hour-old female infant, was admitted to the hospital on October 10, 1952. Both the parents were alive and well. The mother was Rh negative, and the father Rh positive. No studies on the maternal serum had been made during this pregnancy or during the preceding one. A 3-year-old male sibling was reported to be in excellent health. After the birth of the 1st child, the mother received a whole-blood transfusion. The group and Rh type of the transfused blood were not known.

Physical examination revealed a markedly icteric, pale, white infant. Neither edema nor petechiae were present. The patient appeared in fair physical condition. The liver and spleen extended 2 fingerbreadths below the right and left costal margins, respectively.

The temperature was 97.9°F. by rectum, the pulse 120, and the respirations 40.

Examination of the blood showed a red-cell count of 1,530,000 with a hemoglobin of 6 gm. per 100 cc., and a white-cell count of 12,240 with 102 normoblasts per 100 white cells. The Coombs test was +, and the blood was Type A, Rh positive.

A replacement transfusion was begun shortly after admission, the umbilical-vein technic being used. After the introduction of 150 cc. of compatible Type O, Rh-negative blood and the removal of 190 cc. of blood, technical difficulties made the procedure increasingly difficult. Therefore, a cutdown of the right radial artery was performed, from which blood was withdrawn. The umbilical vein was still used for the injection of the Rh-negative blood. A total of 360 cc. of blood was removed, and a total of 320 cc. of blood was injected; 9 cc. of heparin solution (9000 units) was given, and 12 cc. of 10 per cent calcium gluconate solution injected intravenously during the transfusion. The entire exchange procedure occupied a period of 1½ hours.

The patient's condition was extremely poor after the exchange transfusion. During the ensuing 4½ hours, her general condition rapidly deteriorated. The liver and spleen enlarged progressively. At 12:05 a.m. on October 11 she died.

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¶Previously reported by Slotkowski and Hand.[1]

At autopsy the liver edge could be palpated 4 to 6 cm. below the right costal margin, and what was assumed to be the spleen was the same distance below the left costal margin.

Gross examination of the abdominal viscera in situ showed the inferior edge of the liver to be approximately 5 cm. below the right costal margin in the midclavicular line; it weighed 164 gm. (normal weight, 78 gm.) The spleen was diffusely enlarged, its inferior pole extending a distance of 4.5 cm. below the left costal margin in the anterior axillary line; it weighed 35 gm. When the spleen was displaced medially, approximately 40 to 60 cc. of firmly clotted blood was found lying between the leaves of the phrenicolienal ligament. Upon closer external examination a linear rupture of the splenic capsule along the attachments of this ligament was found. Apparently, blood that had escaped from the ruptured spleen before death had dissected its way between the leaves of the phrenicolienal ligament. No fluid blood or clot was found within the abdominal cavity.

Gross examination of the remaining viscera was negative.

Microscopical examination of the lungs demonstrated severe, diffuse, passive congestion accompanied by a minimal amount of intra-alveolar diapedesis.

Marked extramedullary hematopoiesis was present on examination of the spleen. The malpighian corpuscles were greatly reduced in number and size owing to the hematopoietic activity of the organ. On examination of sections taken at the site of rupture there was only a minimal elevation of the capsule. Considerable extramedullary hematopoiesis was present on microscopical examination of the liver.

Microscopical examination of the remaining viscera was negative.

The diagnoses were erythroblastosis fetalis, rupture of the spleen, with hemorrhage into the phrenicolienal ligament, and extramedullary hematopoiesis.

CASE 3. B.W., a female infant was admitted to the hospital on November 30, 1952, 2 hours after a normal, spontaneous delivery. She was dead on arrival. This was the mother's 3d pregnancy. The 2d child was reported to have had a severe anemia due to erythroblastosis fetalis and to have been successfully treated by multiple small transfusions. During this pregnancy, the mother's Rh antibody titer was frequently determined; the day of delivery it was reported to be 1:32.

Post-mortem examination disclosed a moderately icteric, well developed and well nourished infant. No petechiae were present. Minimal edema of the labia and lower extremities was observed. The liver and spleen extended to the level of the umbilicus.

Before any of the abdominal organs were disturbed a firm clot containing 60 to 65 cc. of blood was found situated between the leaves of the phrenicolienal ligament in the left upper quadrant of the abdomen. A 1.5-cm. linear laceration of the splenic capsule along the attachment of this ligament was present. Approximately 40 cc. of a serosanguineous fluid was in the peritoneal cavity.

The spleen was exceptionally soft and friable. It weighed 48 gm.

The liver was greatly enlarged, weighing 234 gm.

The remaining abdominal organs were normal.

The lungs were diffusely and moderately congested with blood. Gross areas of patchy atelectasis were noticed in all lobes.

A fetal type of coarctation of the aorta, measuring 0.2 cm. in length, was found on examination of the heart and great vessels.

The remaining viscera were normal.

Microscopical examination of sections of lung tissue revealed a moderately severe, diffuse, passive congestion. Areas of atelectasis were frequent.

An almost complete absence of malpighian corpuscles was seen on microscopical examination of the spleen. There was considerable vascular congestion of the spleen, and a marked, diffuse extramedullary hematopoiesis. Microscopical sections of the remaining organs of the body were normal.

The diagnoses were erythroblastosis fetalis, rupture of the spleen, with hemorrhage into the phrenicolienal ligament, extramedullary hematopoiesis and a fetal type of coarctation of the aorta.

CASE 4. B.L., a 24-hour-old male infant, was admitted to the hospital from another hospital on March 30, 1954. He was the 2d baby of a 23-year-old mother, whose blood type was not known. His birth weight was 8 pounds, 13 ounces. The pregnancy and labor were uncomplicated.

Physical examination showed an active, well developed, well nourished, well hydrated, markedly icteric and pale infant. The Moro reflex was good. There was a soft systolic murmur along the left sternal border. The lungs were normal to percussion and auscultation. The liver and spleen extended 1 cm. below the right and left costal margins, respectively. The umbilical cord was dry. No edema or petechiae were present. Hemolytic disease of the newborn was the diagnosis on admission.

Examination of the blood disclosed a red-cell count of 3,230,000, with a hemoglobin of 11.2 gm. per 100 cc., and a white-cell count of 26,250, with 59 per cent neutrophils, 22 per cent stab forms, 3 per cent eosinophils, 8 per cent lymphocytes and 2 per cent monocytes. The platelets were normal. The Coombs test was positive.

The patient was Type O, cDE. The mother's blood was unobtainable for typing, and there was no record of typing at the hospital where delivery had been performed.

An exchange transfusion was performed 1 hour after admission, 460 cc. of compatible Type O, Rh-negative blood being given and 500 cc. of the patient's blood withdrawn. Calcium gluconate was administered during the procedure. No heparin was used. The bilirubin level was 23.3 mg. before and 14.8 mg. per 100 cc. after the transfusion, which took 1 hour and 20 minutes.

The hemoglobin was 12.6 gm. per 100 cc., and the red-cell count 3,810,000 on the morning after the exchange transfusion. However, the patient was more sluggish, with a feeble cry and a poor Moro reflex. The liver and spleen extended 3 cm. below the right and left costal margins, respectively. The heart and lungs were normal. No edema or petechiae were present. The bilirubin was 24.6 mg. per 100 cc.

At this time a 2d exchange transfusion was performed, 475 cc. of compatible Type O, Rh-negative blood being administered and 530 cc. of the patient's blood withdrawn. (This deficit was left to maintain a normal venous pressure.) The bilirubin was 16 mg. per 100 cc. after the procedure. The patient looked more alert. Physical examination was as before transfusion.

On April 1 he was severely icteric and lethargic. The Moro reflex was poor. The hemoglobin was 5.8 gm. per 100 cc., and the red-cell count 2,580,000. The bilirubin was 24.6 mg. per 100 cc.

A 3d replacement transfusion was started. After 100 cc. of blood had been withdrawn and replaced by 80 cc. of compatible Type O, Rh-negative blood the patient died, in spite of intracardiac administration of epinephrine and tracheal catheterization.

In the hospital vitamin K, crude liver extract, penicillin and streptomycin were given. He was kept in an incubator, with continuous oxygen.

Post-mortem examination disclosed a markedly icteric, well developed and well nourished infant. The liver edge was palpated 3 cm. below the right costal margin. The spleen was not palpated.

The usual autopsy incision was made. When the abdomen was opened, about 75 cc. of blood was seen lying free in the cavity. The spleen was in its normal position, and there was a disruption of its capsule at its superior tip adjacent to the diaphragm and also at its medial border near the superior tip.

The liver had 2 subcapsular hemorrhages on its anterior surfaces. Otherwise, it was normal. It weighed 175 gm.

The spleen was soft in consistence. It weighed 20 gm. The capsular defects described above were observed. On cut surface the malpighian corpuscles were easily discerned. The splenic pulp bulged from the cut surfaces. The remaining viscera were normal.

Microscopical examination of the bronchi and bronchioles was not remarkable. There was marked atelectasis in many areas, and emphysema in a few. There were severe passive congestion and a small amount of interalveolar and intra-alveolar hemorrhage.

Microscopical examination of the liver revealed a moderate number of lymphocytes, with a few polymorphonuclear leukocytes in the periportal areas. There was considerable congestion, as manifested by large numbers of intact red blood cells lying in the sinusoids.

Examination of the spleen showed the usual number of malpighian corpuscles to be present. These were somewhat reduced in size by engorgement of the red pulp. There was severe passive congestion as manifested by engorgement of the sinusoids by intact blood elements.

Microscopical examination of the remaining viscera was negative.

Discussion

Transfusion teams handling relatively large numbers of erythroblastotic infants are inevitably confronted with the possibility that on occasion their technics have contributed to, rather than prevented, the deaths of infants under their care.

The autopsy findings of ruptured spleen in Cases 1, 2 and 4, all of whom were transfused with considerable care and received heparin intravenously, was most disturbing. In no case can the cause of death be assigned with certainty alone to rupture of the spleen with extravasation of blood into the phrenicolienal ligament, which occurred in Cases 2 and 3. The primary disease, erythroblastosis fetalis, may have been the cause of death as well as the cause of the splenic rupture. Nevertheless, we have been concerned that the splenic hemorrhage may have been provoked by the exsanguination transfusion rather than the erythroblastosis fetalis.

Shortly after Case 2 died, Case 3 arrived in the admitting room dead, apparently from erythroblastosis fetalis. At autopsy a rupture of the splenic capsule similar to that in Case 1 was found. As in Case 2 hemorrhage into the phrenicolienal ligament had occurred.

Case 3 demonstrates that splenic rupture may occur as a complication of erythroblastosis fetalis. When splenic rupture was found after exchange transfusion valid evidence was lacking that the procedure contributed to the splenic rupture. This point is emphasized because misinterpretation of the facts might unjustly implicate a useful therapeutic procedure.

Ante-mortem diagnosis of ruptured spleen in erythroblastotic infants is difficult. First of all, the picture of florid erythroblastosis fetalis distracts one's attention from all corollary findings. Second, as indicated by 2 of these 4 patients, hemorrhage occurs within the confines of the phrenicolienal ligament, thereby reducing the probability that the usual signs of peritoneal irritation will develop.

The pathogenesis of splenic rupture in erythroblastotic infants has been described by Slotkowski and Hand.[1] Of the following predisposing factors mentioned by these authors some operate locally, others systemically, and some in combination:

Extramedullary Hematopoiesis

When the hemopoietic activity of an encapsulated organ is greatly augmented its total volume may increase to such a degree that the viscus and its confining membrane may be stretched to the point of rupture.

Increased Phagocytosis

Increase in this activity of the spleen may produce rupture of the organ and its capsule in a manner similar to that caused by extramedullary hematopoiesis.

Weakening of Supportive Structure of the Spleen

This may occur as a part of an illness. Consequently, less intracapsular tension may be required to produce rupture than in a normal spleen.

Increased Intra-abdominal Pressure

Trauma during delivery may cause increased intra-abdominal pressure. This factor, operative alone or with other factors outlined, is self-explanatory. However, many infants receive artificial respiration without clinical or post-mortem evidence of ruptured spleen.

Damming Back of Blood from the Liver

If this is present it may tend to increase the volume of the spleen and hence its intracapsular pressure.

Increased Blood Volume

The total blood volume may or may not be increased in erythroblastotic infants. Certainly, severe cases are characterized by an increased volume of blood in the venous portion of the circulation. Such a condition may well tend to produce increased pressure within the splenic capsule.

Displacement of the Spleen by an Enlarged Liver

In our experience this is more hypothetical than actual. The enlarged livers that we have encountered at autopsy override the spleen and cause no displacement of it or of its attachments.

Hemorrhagic Tendency

This is due to hypoprothrombinemia, increased capillary permeability or the addition of heparin. The first two apparently exist in infants with severe erythroblastosis. In addition we have frequently noted a marked diminution of the platelets. The injection of heparin does not seem relevant to a discussion of the pathogenesis of splenic rupture. In the first place rupture of the spleen occurs among erythroblastotic infants who have had no heparin. Secondly, rupture of the spleen is not known to occur as a consequence of heparinization. Thirdly, heparin is a rapidly metabolized substance that was given in only moderate quantities to the infants described above.

Earlier in our experiences with erythroblastotic infants we thought that rapid transfusing, or large variations in the blood volume consequent to a single-vein replacement transfusion, might produce rupture of the spleen. We have, however, been unable

to produce experimental rupture of the spleen in an animal subjected to extremely large and rapid contraction of the vascular tree. Therefore, we believe that of all the factors described by Slotkowski and Hand[1] extramedullary hematopoiesis, increased phagocytosis, weakening of the supportive structures and the tendency to hemorrhage are the ones most likely to be responsible for splenic rupture among erythroblastotic infants.

Summary and Conclusions

Four cases of erythroblastosis fetalis with rupture of the spleen are reported. In 1 case the rupture, with hemorrhage into the phrenicolienal ligament, occurred before therapy. In the others replacement transfusion was carried out. All infants died.

Rupture of the spleen does occur in untreated erythroblastotic infants. There is no conclusive evidence that exsanguination transfusion contributes to rupture in infants affected with erythroblastosis fetalis.

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CEREBRAL THROMBOSIS IN YOUNG ADULTS*

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THAT premature vascular degeneration leads to coronary occlusion in young adults is recognized. However, there is a great reluctance to accept a similar etiology for the apoplectic development of focal cerebral signs in young adults. The sudden development of such focal signs as hemiplegia and aphasia in a young patient warrants procedures for detection of a tumor, vascular anomaly, a source of emboli, infectious causes of endarteritis, hematologic disorders or other systemic diseases capable of producing vascular lesions. This investigation is often fruitless. Although there should be a search for all possible etiologic factors that give rise to apoplectic phenomena, it should be emphasized that thrombosis of cerebral arteries attributable to premature vascular degeneration is also a cause of acute neurologic syndromes in young adults.

Evidence that degenerative vascular disease is not limited to patients past forty years of age has been accumulated. Collins, Phillips and Oliver,[1] after monthly canvasses of families in the Eastern Health District of Baltimore to determine causes of chronic disability, reported the presence of arteriosclerosis and hypertension in various age groups. They found these conditions prevalent in a significant number of people under forty years of age (Fig. 1). Irish,[2] reviewing 1000 cerebrovascular lesions in a series of 12,000 autopsies, found that the age distribution of thromboses (Table 1) paralleled that given in the survey of Collins et al.[1] Seventeen patients with cerebral thrombosis were below forty years of age. Ford[3] reported 50 cases of infantile hemiplegia that occurred between three and ten years of age. Ross[4] described 5 normotensive patients between twenty-five and forty-two who had acute focal neurologic syndromes that he postulated to be due to thrombosis of the cerebral arteries. Out of a total of 30 cases of internal-carotid-artery thrombosis, Gurdjian and Webster[5] found 2 in patients between twenty and thirty years and 5 in patients between thirty and forty years of age.

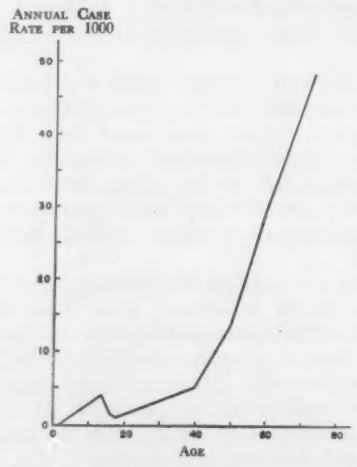

Figure 1. *Hypertension and Arteriosclerosis (Disabling and Nondisabling) in Various Age Groups, Eastern Health District of Baltimore, 1938 - 1943 (Reproduced from Collins et al.[1] with the Permission of the Publishers).*

The vascular abnormalities found in the young people with apoplectic syndromes attributable to premature vascular degeneration resemble those observed

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in adult arteriosclerosis. In 1 of Ford's[5] cases of infantile hemiplegia there was a thrombosis of the middle cerebral artery; all the large cerebral arteries showed intimal plaques composed of connective tissue infiltrated with lipoids, atrophy of the muscularis and fragmentation and reduplication of elastic lamellae. Tuthill[6] reported intimal connective-tissue plaques in a two-year-old patient. Kennedy, Wortis and Wortis[7] found post-mortem evidence of cerebral arteriosclerosis in a thirty-two-year-old normotensive man who had had fourteen episodes of transient hemiplegia on the right in eight weeks. In a group of 19 patients with occlusion of the basilar artery, Kubik and Adams[8] described a thirty-nine-year-old man with generalized atherosclerosis and thrombosis of the basilar artery.

Table 1. *Cerebrovascular Lesions in Various Age Groups.**

Lesion	Patients Under 10 Yr. of Age	Patients 10-19 Yr. of Age	Patients 20-29 Yr. of Age	Patients 30-39 Yr. of Age	Patients 40-49 Yr. of Age	Patients 50-59 Yr. of Age	Patients 60-69 Yr. of Age	Patients 70-79 Yr. of Age	Patients 80-89 Yr. of Age	Patients Over 90 Yr. of Age	Totals
Embolism	4	6	16	17	32	23	23	10	2	–	133
Thrombosis	5	1	2	9	20	70	111	115	26	2	361
Hemorrhage	16	8	27	43	68	97	84	62	11	2	418
Totals	25	15	45	69	120	190	218	187	39	4	912

*Based on Irish.[2]

Although the factors that contribute to the development of arteriosclerosis operate for many years, the clinical effects do not usually manifest themselves until the fifth decade. However, vascular degeneration is known to be accelerated by obesity, diabetes, hypertension and nephrosis. Other factors such as alterations in vasomotor activity, blood viscosity and coagulability, as influenced by life stresses,[9] may participate in the development of vascular lesions. In any event, it is apparent that the clinical syndrome of thrombotic vascular occlusion occurs in young adults and presents the same clinical picture as that seen in older patients with this illness.

Brief case reports illustrative of the syndrome in young adults are presented below. All the cases that we have encountered in the past three years are summarized in Table 2.

Case Reports

Case 1. M.C.P. (B. H. 154 729), a 24-year-old bookbinder, was admitted to the hospital on July 2, 1952, because of aphasia, right-sided sensory impairment and hemiplegia on the right that had begun when he arose on the day before admission. There was no reported loss of consciousness.

The past history revealed an appendectomy at 15 months, "St. Vitus dance" for 1 month at 8 years and jaundice for a few weeks at 16 years of age. The family history was noncontributory except for the death of his mother because of a "stroke" at about 50 years of age.

Physical examination on the day of admission revealed only a spastic right-sided hemiparesis and a mixed type of aphasia. A cardiac consultant found no evidence of cardiac disease. In the hospital a deep venous thrombosis developed in the right lower extremity, but muscle biopsy revealed no primary vascular disease. The hemiplegia gradually improved and the patient was discharged on February 20, 1953, with about 80 per cent return of both motor and sensory function of the right extremities and great improvement in speech function.

Case 2. C.A.H. (B. H. 124 430), a 24-year-old Negro, was admitted to the hospital on March 1, 1950. He stated that in September, 1948, at the age of 22, he awoke with numbness in both hands followed in 1 hour by nausea and vomiting. He lost consciousness for a brief period. On regaining consciousness he found that his left arm and leg were paralyzed. There was gradual improvement after a 3-month period of physiotherapy. In October, 1949, he noticed the onset of convulsive seizures, and he had several grand-mal seizures in January and March, 1950.

Physical examination revealed residua of the spastic left-sided hemiparesis and the hypesthesia and hypalgesia on the left side, but no new findings in the systemic or neurologic examinations. He was discharged on May 2.

Case 3. C.J.S. (B. H. 159 255), a 55-year-old man was admitted to the hospital on October 22, 1952. In 1918, an anomia suddenly developed. He had good recovery of speech over the next 2 years until 1920, when he suffered a "stroke," with sudden onset of paralysis of the right arm and leg and an aggravation of the aphasia. During the next 5 years he regained considerable motor function and had only slight residual impairment of sensation in the right hand. There was also a persistent slight anomia. He had no new complaints until August, 1952, when impaired mentation, staggering gait and increased aphasia suddenly began. Examination revealed astereognosis in the left upper extremity, extinction phenomena on the left side, bilateral hyperreflexia and increased resistance to passive stretch. The mental status and motor function had improved moderately when he was discharged from the hospital on December 5.

Case 4. B.L. (B. H. 141 839), a 29-year-old Negro, was admitted to the hospital on September 14, 1951. He was periodically intoxicated and was erratic in his sleep and work habits. Two days before admission he had noticed a severe headache, which came on suddenly and was not localized to any area. Associated with the headache was a sudden development of numbness of the right side of the face and the left side of the body, hoarseness and diplopia.

The past medical history was noncontributory.

Physical examination revealed 6th-nerve paralysis and a Horner syndrome on the right, sensory impairment over the right side of the face and a contralateral hemiparesis and hypesthesia. The patient was discharged on January 7, 1952, with a good recovery of ocular motility, and of use of the left extremities.

Case 5. H.W.K. (B. H. 145 761), a 34-year-old man, was admitted to the hospital on December 11, 1951. Twelve hours after a bout of alcoholism he suddenly fell, struck his head without losing consciousness and was noted to have a left hemiparesis. A lumbar puncture shortly after the onset was reported as being entirely normal. At the onset bizarre behavior characterized by senseless laughter and aggressive activity developed. During the hospital course there was a gradual improvement in behavior and use of the extremities.

The past history revealed that the patient had been a prisoner of war in Germany. He had had a surgical repair of a gunshot wound of the abdomen during World War II. He had pneumonia in 1951. He had gone without sleep for a long period to drive a trailer truck across the country, and he had worked long hours without assistance to achieve financial independence. He was discharged on April 9, 1952, with a mild residual hemiplegia.

CASE 6. F.W.C. (B. H. 150 645), an 18-year-old boy, suddenly lost consciousness for a short time on November 13, 1948. On regaining consciousness, he was found to be aphasic and to have a hemiparesis and a hemisensory syndrome on the left. Lumbar puncture on admission revealed crenated red blood cells, normal spinal-fluid pressure and grossly bloody fluid. However, this was attributed to trauma during the procedure because, 48 hours after admission, when trephination was performed to ascertain the cause of progressive drowsiness, an area of encephalomalacia of the cerebral cortex over the right frontal and parietal lobes was found, but there was no evidence of any intracerebral, extradural, subdural or subarachnoid hemorrhage. The function of the extremities gradually improved. The patient had several convulsions after the onset of the hemiplegia. Arteriograms in January, 1949, and February, 1950, disclosed narrowing of the right internal carotid artery and straightening of the carotid siphon. A pneumoencephalogram in March, 1950, revealed slight dilatation of the right lateral ventricle, with no displacement of the interventricular septum. When the patient was last seen in March, 1953, there was great improvement in power and function of the left extremities. The convulsions were controlled by medication.

CASE 7. D.O. (B. H. 146 394), a 34-year-old woman, was admitted to the hospital on December 19, 1951. She had been in excellent health until November 14, when, while playing golf, she had a sudden onset of weakness and staggering gait, and numbness of the right side. She collapsed because of a paralysis of the entire right side of the body.

Physical examination demonstrated a mixed aphasia and a right-sided hypesthesia and hemiplegia. An arteriogram showed occlusion of the left internal carotid artery, and surgical exploration revealed a thrombosis of the same artery. She was discharged from the hospital on October 3, 1952, after gradual improvement in the use of the extremities and in language function. There were severe residua 1 year after the onset, however.

TABLE 2. *Summary of Cases of Cerebral Thrombosis.*

Case No.	Age at Onset	Follow-up Period	Artery Occluded	Blood Pressure	Electrocardiogram	Fasting Blood Sugar	Cholesterol	Cerebrospinal-Fluid Total Protein	Air Encephalogram	Arteriogram
	yr.					mg./100 cc.	mg./100 cc.	mg./100 cc.		
1	24	10 mo.	Lt. middle cerebral	120/70	Normal	88	183	36	Normal	Normal
2	22	5 yr.	Rt. middle cerebral	118/80	—	98	—	29	Cortical atrophy on rt.	Occlusion of rt. middle cerebral artery
3	23	32 yr.	Lt. middle	130/80	Normal	77	253	51, 72, 48, & 12	Enlarged lateral ventricle	—
4	29	15 mo.	Lt. postero-inferior cerebellar	120/78	Normal	91	212	—	—	—
5	34	1 yr.	Rt. middle cerebral	120/70	—	96	—	72	Normal	—
6	18	4 yr.	Rt. middle	120/80	—	91	—	39	Enlarged lateral ventricle	Narrow rt. internal carotid artery
7	34	17 mo.	Lt. internal carotid	120/80	Normal	—	—	—	—	Occlusion of lt. internal carotid artery
8	29	14 mo.	Branch of rt. postero-cerebral	110/80	—	—	—	54	—	Normal
9	25	30 mo.	Rt. middle cerebral	120/80	Normal	—	208	29	Normal ventricle	Normal
10	34	15 mo.	Rt. internal carotid	110/70	Normal	90	—	53	—	Narrow rt. internal carotid artery
11	37	7 mo.	Rt. & lt. middle cerebral	120/80	Normal	88 & 117	168	53 & 38 54 & 32	—	—
12	27	1 mo.	Lt. middle cerebral	130/80	Normal	—	166	45	Enlarged lt. lateral ventricle	Anterior cerebral artery displaced by cerebral swelling
13	28	3 mo.	Basilar	140/80	Normal	—	—	50	Normal	—

CASE 8. F.F.G. (B. H. 148 683), a 28-year-old man, was admitted to the hospital on February 18, 1952, because of the sudden onset of severe headache localized to the right temporal region and described as sharp and persistent. At the same time he had vomiting, diplopia and weakness of the left side of face, arm and leg. Physical examination 1 week after the onset of his illness, disclosed a hemiparesis, slurred speech, diplopia and somnolence. There was no past history of trauma or other illness. The diplopia and somnolence improved a few days after admission; there was gradual improvement in power of the left extremities, and the dysarthria had disappeared at the time of discharge on June 20. Ten months later there was slight hemiparetic gait and impairment of rapid movements, but good strength of the affected extremities.

CASE 10. C.S.T. (B. H. 166 091), a 34-year-old Negro, was admitted to the hospital on May 19, 1953. After he went to bed on September 24, 1952, a severe right-sided headache suddenly developed, persisting for several hours. He then suddenly noted that his speech was thick and that his left upper and lower extremities were paralyzed. Examination shortly after the onset revealed mild clouding of the sensorium, a spastic hemiparesis on the left and an incomplete left-sided homonymous hemianopsia. The gen-

eral physical examination and examination of the blood and spinal fluid were negative; the sedimentation rate and glucose tolerance curve were normal, but an arteriogram demonstrated occlusion of the right internal carotid artery. The electroencephalogram, which was abnormal at first, had gradually improved by the time of discharge on June 19; gradual improvement in neurologic status was also apparent, but he still had a moderate hemiparesis 15 months after the onset and he had 1 grand-mal seizure.

The past history is significant in that he had had episodic severe right-sided headaches since 1942. Early in 1952 a headache had been preceded by severe bilateral negative scotomas. For several months before the onset of the hemiplegia he permitted himself only 3 or 4 hours of sleep each night because of the burdens of attempting to participate in a program of college training and at the same time to support his family.

CASE 13. D.F., a 28-year-old man, after consuming a small amount of alcohol, suddenly lost consciousness for a few minutes on December 24, 1951, for the first time in his life. After regaining consciousness he went home unassisted. At 2 o'clock on the following morning he was found to be unconscious and having generalized convulsions. The convulsions continued until he was admitted to the hospital in status epilepticus several hours later.

The blood pressure was 140/90, the pulse was 120, and the temperature 100.8°F. Except for the evidences of seizure there were no focal abnormalities. The patient remained unconscious after the onset of the seizures.

On December 31 a ventriculogram was taken, but no abnormalities of the ventricles or of the ventricular fluid were noted. Subsequent spinal-fluid examinations were entirely negative. An electroencephalogram was normal. Thirty-five days after the onset it was observed that although he blinked in response to visual stimuli, there was a lack of conjugugate eye movements. Tonic neck reflexes were also demonstrated.

He never regained consciousness and died 80 days after the onset of his illness. Post-mortem examination revealed a few small atheromatous plaques on the intimal surface of the aorta. The heart valves, myocardium and coronary vessels were normal. There was a white plaque at the terminal portion of the basilar artery, and the lumen of this portion of the vessel was narrowed. Sections of the basilar artery showed fibrous thickening of the intima with a hemorrhage dissecting the intima from the media. In another area of the same artery there was a fibrous thickening of the wall and a papillomatous elevation of the intima. No inflammatory changes of the vessel were evident. There was a fibrous thickening and occlusion of 2 small arteries adjoining the basilar artery, as well as a fibrous thickening of small arteries of the cerebral cortex. There was a large area of anemic necrosis of the pons extending bilaterally from the floor of the fourth ventricle to the base. The region of the substantia nigra was similarly affected bilaterally.

DISCUSSION

In this group of 13 patients a sudden apoplectic onset of focal neurologic signs without any other discernible neurologic or systemic disease, occurred at eighteen to thirty-seven years of age. The most common manifestation of the ictus was hemiplegia, but states of mental clouding, somnolence, aphasia, diplopia and convulsive seizures also occurred. The course in all but the fatal case was marked by progressive improvement, but residual hemiparetic defects persisted. Therefore, the symptoms and signs of an acute onset of a focal cerebral lesion with subsequent progressive improvement are identical to the characteristics of the "stroke" syndrome of cerebral thrombosis in older people. However, since it is considered unusual for persons below the age of forty to have severe primary vascular degenerative disease of the brain, it is important that other possible etiologies of acute focal neurologic lesions be carefully investigated. In the differential diagnoses of the cases discussed above other causes of vascular lesions of the brain were consequently considered. These might be emboli from rheumatic heart disease or pulmonary disease. Vascular occlusion attributable to syphilis, periarteritis nodosa, or disseminated lupus erythematosus, or vascular degeneration associated with diabetes and hypertension could also be responsible for the acute development of encephalomalacia. Hemorrhage into the brain, either from a ruptured aneurysm or from a highly vascular necrotic tumor, might produce a similar disability. Finally, blood dyscrasias either with increased clotting tendencies, such as polycythemia vera, or with hemorrhagic tendencies might also cause sudden focal brain lesions. These were eliminated as possible causes by the following studies.

It was noted that the blood pressures, pulse rates and cardiac rhythms of all the patients were normal. Electrocardiograms taken in 6 patients were also normal. X-ray examinations of the chest were negative, except for an old pleuritis in 1 patient. These facts, combined with the negative physical examination of the heart and lungs, tend to eliminate emboli and hypertension as being responsible for the lesions.

Serologic reactions for syphilis in the blood and spinal fluid were negative in all patients, and no history of syphilis was available. Therefore, the probability of syphilitic vascular disease was minimal. The repeatedly normal red-cell and white-cell counts and sedimentation rates and the afebrile course were against the possibility that blood dyscrasias or infectious agents caused the vascular lesions. Also, repeated blood cultures failed to reveal a septicemia.

In 6 cases tested blood cholesterol levels were normal. In 9, fasting blood sugars were normal, and in all 13 cases the urine gave no chemical reaction for sugar. Hence, diabetes, which is capable of accelerating vascular degeneration, was not involved in the disease.

Spinal-fluid examinations were performed in 11 cases at the onset of the disability in an effort to detect any bleeding or changes produced by a tumor or aneurysm. Bloody spinal fluid was reported in only 1 case, in which surgical exploration demonstrated an area of encephalomalacia without bleeding. The only spinal-fluid abnormality in the other 10 cases consisted of minor increases of total protein. In no case was the spinal-fluid pressure increased above normal ranges.

Arteriography, performed in 7 cases in a search for a carotid-artery aneurysm, vascular anomaly or tumor, was negative in all. In Cases 2, 6, 7 and 10, there was evidence of either occlusion or narrowing of the internal carotid artery or its branches. Six pneumoencephalograms and 2 ventriculograms were performed, but there was no evidence of any space-occupying lesion such as a neoplasm or intracerebral

hematoma. In fact, whenever an abnormality was noted, it was indicative of a focal atrophy secondary to encephalomalacia. Four patients had mild dilatation of one of the lateral ventricles, and in 1 of these the area of encephalomalacia was found after trephination of the skull.

The prognosis after a cerebrovascular occlusion in a young adult seems to be good. There is generally a spontaneous improvement in the functions affected. Furthermore, 1 of the patients survived for thirty-two years after the initial attack. However, 2 patients have had recurrent though nonfatal vascular lesions. The 1 fatal case occurred in a patient with a thrombosis of the basilar artery.

It may be significant that, in several patients, the illness developed in settings of stressful life situations. In at least 6 cases there were histories of strong strivings for success, with consequent self-deprivation and lack of rest, alcoholism or severely disturbing sexual conflicts. It is well known that certain stressful situations contribute to the development of coronary occlusion by altering blood-clotting mechanisms and blood viscosity or increasing resistance to blood flow. It is possible that the same mechanisms were involved in these young patients and contributed to the development of the cerebrovascular lesions. Ross,[4] similarly, concluded that emotional factors contributed to the development of cerebrovascular lesions in a young physician in whom dysphasia developed two hours after a plunge into cold water.

These clinical observations support the concept that cerebral thromboses in young adults are due to cerebrovascular degeneration, but further confirmation of this depends on additional post-mortem material.

Summary

Thirteen cases of acute cerebrovascular lesions in young adults of eighteen to thirty-four years of age are presented. Diagnostic procedures failed to give evidence of hemorrhage, emboli, hypertension, neoplasm, diabetes, blood dyscrasias, congenital aneurysm or other vascular anomalies.

The thromboses in these cases were attributed to occlusive vascular disease such as arteriosclerosis.

The degree of disability varied, depending on the site and size of the vessel occluded.

The course was marked by improvement in each case, and 1 of the patients was alive thirty-two years after the first episode of vascular occlusion.

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NONBACTERIAL REGIONAL LYMPHADENITIS ("CAT-SCRATCH FEVER")*

An Evaluation of the Diagnostic Intradermal Test

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During the period October, 1953, through February, 1954, the diagnosis of nonbacterial regional lymphadenitis was made in 18 patients at the Massachusetts General Hospital. An intradermal-test antigen was used in each of the cases, giving rise to theoretical questions concerning the sensitivity and diagnostic significance of the intradermal test. Since the literature does not contain any reports of an extensive study of tests with this antigen in normal people an investigation of its value was carried out. The present report summarizes the results obtained with a limited supply of antigen and indicates the need for further study of the problem.

Nonbacterial regional lymphadenitis, usually a benign disease, has been reported from many areas of the world. Studies, as summarized by Debré and Job,[1] have revealed the following data. Although the causative agent has not been isolated, the disease has been transmitted to human volunteers and monkeys. The pathology of the involved lymph nodes follows a definite but not pathognomonic pattern. In about 50 per cent of the reported cases a history of contact with cats, including cat scratches, has been elicited. There is a characteristic, seldom fatal, clinical course; regional lymphadenitis follows a primary lesion at or near the site of trauma. Positive complement-fixation tests for lymphogranuloma venereum have been mentioned in variable percentages by different investigators. Broad-spectrum antibiotics

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have been described as hastening recovery in some cases. Lastly, there is a "specific" intradermal diagnostic test in which a tuberculin-type hypersensitivity reaction is evoked by the inoculation into a patient of heated pus aspirated from suppurative lymph nodes of persons suffering from the disease.

In addition to these experimental and clinical observations, certain impressions and hypotheses have arisen. Thus, the etiologic agent is assumed to be a virus of the clamydozoaceae family that gains entry to the body through a traumatic break in the skin due to cat scratches, splinters, thorn pricks and so forth. The disease is considered to be more prevalent than case reports in the literature indicate, especially since many new cases are discovered once the diagnostic acumen in a community is whetted by an initial diagnosis of the malady.

Because of its frequent association with contact or scratches by cats, the disease is usually designated "cat-scratch disease" or "cat-scratch fever." However, no cases have been reported in which a sick cat has been involved, and none of the cats that have been skin tested have given positive reactions. Because the cat seems to serve merely as inoculator of the causative agent it seems preferable to refer to the disease by the title accepted by the Committee on Standard Nomenclature of Diseases and Operations: "Nonbacterial regional lymphadenitis (cat-scratch fever)." The official code number for this is now 55.-130; the international equivalent is 694, as listed in the supplement to the *Standard Nomenclature of Diseases and Operations*.[2]

"Specific" diagnosis depends on a positive intradermal test in a patient who has characteristic signs and symptoms. Other criteria usually applied to etiologic diagnosis cannot be used in this illness — for example, isolation and identification of the etiologic agent, serologic tests and pathognomonic pathologic findings. Since the specificity of the diagnosis, therefore, depends heavily on the intradermal test, it was of interest to us to investigate this reaction with the subjects and materials available. A brief summary of our clinical experience with the condition is followed by a description of the experimental work.

TABLE 1. *Clinical Data in 18 Cases of Nonbacterial Regional Lymphadenitis.*

CASE NO.	AGE	SEX	SITE OF SCRATCH OR PAPULE	SITE OF INVOLVED NODES	DURATION OF ADENITIS	SUPPURATION	FEVER	MALAISE	LABORATORY TESTS*	SKIN TEST FOR NONBACTERIAL LYMPHADENITIS
	yr.				*mo.*					
1	7	M	?	Left femoral triangle	2	+	+	+	–	+
2	10/12	M	Finger	Axilla	2	+	+	+	–	+
3	14	M	?	Anterior cervical, paratracheal	3	+	+	+	–	+
4	11	F	Wrists	Supraclavicular	4	–	–	+	–	+
5	18	M	Thigh	Left femoral triangle	3	+	+	+	–	+
6	52	F	Finger	Axilla	?	–	–	+	–	+
7	7	F	?	Submaxillary	6	–	+	+	–	+
8	49	F	?	Submental	3	–	+	+	–	+
9	12	F	Conjunctiva	Preauricular & anterior cervical	2	–	+	+	–	+
10	23	F	Scalp	Postauricular & posterior cervical	1	–	+	–	–	+
11	7	M	Finger	Axilla	3	+	+	+	–	+
12	4	M	Finger	Axilla	2	–	+	+	–	+
13	5	F	Hands	Submental	2	–	+	+	–	+
14	10	M	Finger	Axilla	2	–	–	–	–	+
15	11	M	?	Preauricular & infra-auricular	1	–	+	–	–	+
16	11	M	Conjunctiva	Preauricular	2	–	+	+	–	+
17	3	F	?	Submental	1½	–	+	+	–	+
18	9	F	Lacrimal glands	Preauricular	2	–	+	+	–	+

*Includes tuberculin test, agglutination tests for tularemia, brucellosis & heterophil antibody, examination of peripheral-blood smears & skin test for lymphogranuloma venereum. Agglutination tests for heterophil antibodies not performed in Cases 1 & 2.

CLINICAL DATA

The clinical characteristics usually observed in nonbacterial regional lymphadenitis and the frequency with which they were encountered in this series are summarized in Table 1.

Lymphadenopathy

This finding was present in each of the cases studied. It was usually the presenting symptom and the major therapeutic concern. Though the axillary lymph nodes were most frequently involved, the widespread anatomic location of the nodes, as observed from case to case, was impressive, and in-

cluded unusual sites of adenopathy such as the preauricular and supraclavicular nodes. In 1 case, in which only the anterior cervical chain seemed to be involved, extensive involvement of the deeper lymph nodes with tracheal impingement was seen at operation. As a rule the regional lymph nodes immediately proximal to the papule were not diseased, and in a few cases two or more proximal groups of nodes were spared whereas more distal nodes were affected. For example, in Case 4 there was swelling of the supraclavicular node on the same side as the papule on the wrist, but the epitrochlear and axillary nodes were not palpable. This sort of variation from the usual clinical picture may cause confusion in diagnosis, for in such a case the question of cancer comes to mind. The size was variable, the diameter ranging from 1 to 10 cm. Likewise, there was a variation in the degree of sensitivity and consistence, depending to some extent on whether or not suppuration was developing. Suppuration occurred in approximately a third of the cases, being recognized by the usual signs of tenderness, dermal erythema and fluctuation. A third of these regressed without surgical intervention whereas the remainder required drainage. Cultures of the evacuated material were invariably found to be bacteriologically sterile even though the pus was considered by several surgeons to be typical of that seen in staphylococcal infections. Perhaps the single most characteristic finding was the long duration — three weeks to six months — of the adenopathy. As a rule, the inflammation in the lymph node subsided gradually, and by the end of two months the node had completely disappeared. In 1 case, however, the node had almost disappeared at the end of four months, but suddenly enlarged again and persisted for an additional two months.

Primary Lesion

At the time of the first examination a primary papule was discovered in only 9 patients. Half the patients gave a history of a cat scratch at the site where the primary papule developed; in the others it was not possible to elicit a history of a traumatic break in the skin either from animal contacts or from injury with an inanimate object. An interesting example in which an animate or inanimate object may have been the source of infection was that of a woman in daily contact with cats, who cut her finger when opening a tin of cat food and then handled the cat. In a few days a primary papule developed at the site of injury, and about a week later regional lymphadenopathy was noted.

The average period between the appearance of the primary papule and the development of regional lymphadenopathy was ten days.

Fever

Elevations of temperature were observed in 15 patients. However, these were generally low grade, only occasionally rising above 101°F. An equal number had a mild loss of well-being and generalized malaise.

Findings in Peripheral Blood

Examination of the peripheral blood usually revealed only a slight leukocytosis, but in 1 case the white-cell count reached 55,000 and there was a marked shift to the left in the polymorphonuclear leukocytes. In the only case in which bone-marrow studies were performed, myeloid hyperplasia, with a surprising bone-marrow eosinophil level of 15 per cent, was observed. At the same time the peripheral blood contained 2 per cent eosinophils.

Other Laboratory Data

Laboratory tests were performed on all patients for detection of other diseases that were considered in the differential diagnosis, such as tuberculosis, tularemia, brucellosis, lymphogranuloma venereum and infectious mononucleosis. These tests were uniformly negative.

Age Range

The age range was ten months to fifty-two years. Fifteen of the 18 patients were in the pediatric age group, and the remainder were adults. The sexes were about evenly affected. To our knowledge the ten-month-old infant was the youngest to be described in the literature. In Case 13 a transitory anaphylactoid purpura developed during the course of the infection.

Experimental Data

Preparation of Skin-Test Antigen

Antigen for the performance of intradermal testing was prepared in the manner recommended by Daniels and MacMurray.[8] Three patients served as donors. On surgical indication, pus was aspirated from a lymph node under aseptic conditions from each of the 3 patients, delivered to the bacteriology laboratory and stored either at 4°C. or at −20°C. until bacteriologic cultures proved sterile. The pus was diluted 1:5 in 0.85 per cent sterile sodium chloride and heated for an hour in sterile, glass-sealed Pyrex tubes submerged in a water bath at 56°C. The tubes were then refrigerated and heated for a second time on the following day at the same temperature for the same length of time. The three test antigens were again cultured aerobically and anaerobically and found to be sterile before use in the intradermal test. No preservatives were added. After the potency of the three antigens had been established a pool was made of approximately equal parts of each. This pool was assayed in volunteers and found to be potent. The results of these assays, with exact measurements, are presented in Tables 2 and 3.

Specificity of Skin-Test Antigen

Three intradermal-test antigens were prepared for use in this study according to the method just described. The 3 patient donors of the test material had illness characteristic of nonbacterial regional lymphadenitis. This diagnosis was confirmed by positive intradermal tests performed with antigen supplied by Dr. Worth B. Daniels.

The preliminary tests of these antigens were carried out on 8 patients with a clinical diagnosis of nonbacterial regional lymphadenitis as well as on a group of 11 normal subjects. The results of these tests are presented in Table 2, which demonstrates that the Massachusetts General Hospital antigens used in this survey fulfilled the following requirements for this type of intradermal test:

The test materials were obtained from patients in whom the diagnosis was established by clinical findings as well as by positive intradermal testing.

The antigens caused positive reactions in patients in whom the clinical diagnosis was consistent with that of nonbacterial regional lymphadenitis; in several of these patients the clinical diagnosis was substantiated by positive reactions with skin-test antigens obtained from another source.

The antigens caused a negative reaction in the majority of control subjects with no history of nonbacterial regional lymphadenitis.

Control Subject 11 gave strongly positive reactions to all three Massachusetts General Hospital antigens (Table 2). The occurrence of this unexpected reaction in the absence of present or past history of signs and symptoms initiated the present investigation.

TABLE 2. *Preliminary Evaluation of M.G.H. Skin-Test Antigens.*

	Evaluation No.	M.G.H. Antigen*			Proved Antigen†			
		no. 1	no. 2	no. 3	no. 4	no. 5	no. 6	no. 7
Patients:								
	1‡	Not tested	Not tested	Not tested	8 40	8 30	6 35	Not tested
	2‡	Not tested	Not tested	Not tested	5 20	Not tested	Not tested	Not tested
	3‡	5 20	14 40	5 15	4 5§	Not tested	Not tested	Not tested
	4	6 20	10 40	8 25	Not tested	Not tested	Not tested	4 5
	5	8 10	10 30	8 25	6 30	Not tested	Not tested	Not tested
	6	+	Not tested	Not tested	+	Not tested	Not tested	Not tested
	7	8 16	12 35	Not tested				
	8	10 30	15 40	4 8				
	9	4 10	8 18	6 11				
	10	6 12	4 7	5 7				
Controls:								
	1	Not tested	Not tested	Negative				
	2	Negative	Negative	Negative				
	3	Negative	Negative	Negative				
	4	Negative	Negative	Negative				
	5	Negative	Not tested	Not tested				
	6	Negative	Negative	Negative				
	7	Not tested	Not tested	Negative				
	8	Not tested	Not tested	Negative				
	9	Not tested	Not tested	Negative				
	10	Not tested	Not tested	Negative				
	11	6 13	12 30	7 20				

*1st figure refers to size of papule (mm.) & 2d to area of erythema (mm.); + indicates positive reaction but exact measurement unavailable.
†Kindly supplied by Dr. Worth B. Daniels.
‡Donor of correspondingly numbered M. G. H. antigen.
§Patient received only 0.02 cc. instead of 0.1 cc. of this antigen.

Interpretation of the Skin Test

In the test 0.1 cc. of the antigen was injected into the skin of the forearm of the subject. An "immediate" reaction — wheal and flair — usually developed within ten minutes and persisted for as long as twenty-four hours in most cases. In all cases, however, this nonspecific reaction had disappeared forty-eight hours after inoculation when the specific reactions were read. A reaction was considered to be positive if there was an indurated papule measuring 4 mm. or more, surrounded by a zone of erythema about 1 cm. or more in diameter. In subjects in

whom positive reactions were not observed at forty-eight hours, it was often impossible even to determine the site of inoculation.

In the upper part of Table 2 are recorded measurements of skin reactions observed in the 8 patients on whom the Massachusetts General Hospital antigens were first assayed. Six of the 8 patients tested reacted positively to each of the three antigens; 1 patient had only two of the antigens applied and reacted positively to both, and another had one of the antigens applied and reacted positively to it. Those in whom antigens from other sources gave positive reactions also reacted in a positive manner with Massachusetts General Hospital antigens. No subject reacted to only one antigen when more than a single antigen was administered. This statement applies both to control subjects and to patients.

It is apparent from an inspection of the measurements listed in Table 2 that some of the reactions encountered were 1 mm. below the minimum measurements of 5 mm. for the papule and 10 mm. for the erythema arbitrarily established by other workers. Nevertheless, our studies show that when multiple antigens are used a given patient may have a minimum reaction to an antigen from one source and simultaneously have a strikingly larger reaction to an antigen from another source. For this reason we have designated 4 mm. as the minimum size of the papule that could be interpreted as a positive reaction. A papule of this size, with surrounding erythema, observed forty-eight hours after administration of the antigen is a definite, easily observed entity and is readily distinguished from the residual unraised trauma or discoloration that infrequently persists after administration of the skin-test material. Clinical experience further indicates that the size of the reaction is unrelated to the severity of the illness.

As shown below, an appreciable number of healthy subjects gave positive reactions to the Massachusetts General Hospital antigens. Table 3 compares the sizes of the positive intradermal reactions encountered in the group of 18 patients who were clinically ill with nonbacterial regional lymphadenitis and in the healthy controls. The wide variation in the size of reaction in different persons tested with the same antigen as well as the variation in size of reactions evoked in the same subject by different antigens is apparent. Antigen 8, a pool of antigens 1, 2 and 3, usually caused smaller reactions than the separate antigens comprising the pool.

Inspection of the reactions occurring in the groups of subjects reveals that it is impossible to separate, by size of reactions, those currently ill with the disease from those who had a positive skin test in the absence of illness.

An unusual type of reaction to the intradermal antigens was encountered in 5 subjects in whom the skin test was completely negative in forty-eight hours.

TABLE 3. *Comparison of Skin Reactions in Patients and in Subjects Healthy at the Time of Testing.*

	PATIENTS*								HEALTHY SUBJECTS*		
CASE NO.	M.G.H. ANTIGEN NO. 1	M.G.H. ANTIGEN NO. 2	M.G.H. ANTIGEN NO. 3	ANTIGEN NO. 4†	ANTIGEN NO. 5†	ANTIGEN NO. 6†	ANTIGEN NO. 7†	ANTIGEN NO. 8‡	SUBJECT NO.	ANTIGEN NO. 1	ANTIGEN NO. 8
1				8 40	8 30	6 35			1	12 30	
2				5 20					2		5 7
3	5 20	14 40	5 15	4 5					3		5 10
4	6 20	10 40	8 25				4 5		4		7 10
5	8 10	10 30	8 25	6 30					5		4 9
6	+			+					6		4 6
7	8 16	12 35						10 35	7		8 12
8	10 30	15 40	4 8		8 35				8		5 10
9	4 10	8 18	6 11					6 9	9		4 9
10	6 12	4 7	5 7					6 8	10		7 12
11				12 35					11	5 15	5 15
12					8 30				12		10 20
13					8 35						
14								6 12	§		6 9
15								6 10	§		15 40
16								6 13	§		10 20
17	4 5	3 5	6 8						§		5 7
18			5 10						§		? ?

*1st figure refers to size of papule (mm.), & 2d to area of induration (mm.); + indicates positive reaction but exact measurement unavailable.
†Kindly supplied by Dr. Worth B. Daniels.
‡M. G. H. antigen pool.
§Reactions appearing several days after usual type of reaction should have occurred — listed as negative (see text).

In these subjects induration and erythema developed five to nine days after administration of the antigens at the site of inoculation. These reactions were indistinguishable in character from a true-positive reaction, differing only in the time after which they became apparent. They occurred in 3 animal-hospital personnel and in 2 Massachusetts General Hospital personnel. Because they were called to our attention by subjects interested in the study it is believed that more such reactions might have occurred in other subjects who were not observed beyond the single skin-test reading forty-eight hours after the administration of the antigen.

Since the reactions at best may be considered only equivocal we have chosen to interpret them as negative, and they therefore appear as negative in Table 3.

Although similar reactions have been described after the administration of nonbacterial regional lymphadenitis intradermal antigens their significance cannot be appreciated since this type of reaction is unlike any presently recognized expression of bacterial hypersensitivity. However, the appearance of induration after a delay of approximately a week is analogous to the type of reaction elicited by Kveim antigen in patients with sarcoidosis.[4] Whether or not there is any relation between these two phenomena, however, remains a matter for speculation.

Groups Studied

Several groups of subjects were studied in connection with the intradermal test.

Group I (patients with nonbacterial regional lymphadenitis). All the patients, at the time of the investigation, had signs and symptoms. In each case other factors that might have caused the present illness were eliminated by appropriate laboratory tests (Table 1). All patients reacted positively to one or more skin-testing antigens.

Group II (members of families of Group I patients). During the initial studies with the antigens prepared in this hospital the family member who accompanied the patients to the hospital was also skin tested. Later, skin testing was extended to all available members of the families of patients, at their homes. This group consisted of 38 siblings and parents of the patients.

Group III (family controls). The 21 subjects comprising this group represented all or part of 9 families in whom there was no known history of nonbacterial regional lymphadenitis.

Group IV (animal-hospital personnel). The 21 subjects comprising this group were all employed at the same animal hospital. All had frequent contact with cats as well as with other animals, and most admitted to being scratched by cats as well as by other animals. Three had had illnesses in the past consistent with the diagnosis of nonbacterial regional lymphadenitis. Of these illnesses 1 had been diagnosed as nonbacterial regional lymphadenitis,* another as tularemia,† and the third as undifferentiated acute lymphadenitis.‡

Group V (institutional controls). To study a group of subjects similar in makeup to that at the animal hospital, the co-operation of a like number of persons employed at this hospital was obtained. This group of 22 consisted of doctors, nurses, laboratory technicians and ward helpers, several of whom were intimately associated with some of the patients during their illnesses with nonbacterial regional lymphadenitis.

TABLE 4. *Results of Intradermal Test.*

GROUP	PATIENTS ILL WHEN TESTED		SUBJECTS WITH PAST HISTORY		PATIENTS WITH NO PAST HISTORY	
	TOTAL NO.	NO. POSITIVE	TOTAL NO.	NO. POSITIVE	TOTAL NO.	NO. POSITIVE
I	18	18 (100%)	0	—	0	—
II	0*	—	0	—	38	4 (10.5%)
III	0	—	0	—	21	1‡(4.8%)
IV	0†	—	3	2 (66.7%)	18	4 (22.2%)
V	0	—	0	—	22	1‡(4.5%)
Totals	18	18 (100%)	3	2 (66.7%)	99	10 (9.9%)

*Group I included 2 cases representing 2d concurrent infections in respective families.

†Group I included employee of animal hospital with signs and symptoms when tested.

‡Subjects sisters but members of separate households at time of skin test.

Results of Skin-Test Survey

One hundred and twenty subjects were given intradermal tests with one or more antigens or with a pool of the three antigens. Table 4 gives the status of the subjects in relation to nonbacterial regional lymphadenitis. All the patients, at the time of testing, reacted in a positive manner. Two of the 3 subjects with a past history of nonbacterial regional lymphadenitis reacted in a positive fashion. Among the remaining 99 subjects, 10 positive skin tests were encountered, a prevalence of 10.1 per cent.

An analysis of the occurrence of positive reactions in healthy persons reveals that positive reactors were unevenly distributed among the various groups. Thus, 4 of 38 (10.5 per cent) members of families of patients (Group II) had positive reactions to the intradermal-test antigen whereas only 1 of 21 (4.8 per cent) members of normal families (Group III) reacted in a positive manner. When personnel of the

*The clinical diagnosis was confirmed in 1952 by means of a positive reaction to an antigen prepared by Dr. Lee Foshay of Cincinnati. The patient had a negative reaction in 1954 to the antigen used in this study.

†The clinical diagnosis of tularemia was made in 1944 without bacteriologic or serologic support. The patient had a positive reaction in 1954 to the antigen used in this study.

‡This patient was seen in the Out Patient Department of the Massachusetts General Hospital in 1953. The clinical history was typical of nonbacterial regional lymphadenitis, including the finding of sterile pus in an axillary gland. The antigen was not available at that time for skin testing, but the patient had a positive reaction in 1954 to the antigen used in this study.

animal hospital (Group IV) were tested, 4 of 18 (22.2 per cent) had positive skin reactions in contrast to the single positive reaction encountered among 22 employees (4.5 per cent) of the Massachusetts General Hospital (Group V) tested with the same antigen. It is noteworthy that the only 2 positive reactions encountered in the control groups (Groups III and V) occurred in sisters.

Thus, there was a greater prevalence of positive reactions in Groups II and IV than in the corresponding groups that served as controls, suggesting that the former may indeed be "high-risk" prospects for nonbacterial regional lymphadenitis. However, the size of each group was not large enough to permit the results within the groups to be considered statistically significant. Subjects in Group II had continued association or contact with cats and were frequently scratched in the course of their occupation. Subjects in Group IV were exposed to the same domestic environment, including the family cat, as the respective members of their families who became ill. Moreover, 2 simultaneous infections occurred in each of 2 families; also, an employee at the animal hospital was ill at the time that group was skin tested.

A further indication that definite "high-risk" conditions for nonbacterial regional lymphadenitis exist is the fact that the only 2 normal subjects (Groups III and V) who had positive skin tests were sisters, although at the time of the test they were members of separate households.

Discussion

The fairly large percentage of apparently normal subjects reacting in a positive manner to the skin-testing antigen supports the view that inapparent cases do occur and result in the same type of dermal hypersensitivity as that which follows frank infections. Hence, the demonstration of positive reactions with skin-testing material, as presently prepared, is of little value in diagnosis in the absence of well defined clinical signs and symptoms. More definite diagnosis awaits the development of a serologic test by which an increase in antibodies in the serum of the patient might be demonstrated during the course of the illness under study. It is tempting to speculate whether or not the subjects who reacted in a positive manner during this study are immune to nonbacterial regional lymphadenitis. No cases of second attacks have been reported in the literature as might be expected if the causative agent is indeed viral.

Summary

Eighteen cases of nonbacterial regional lymphadenitis are briefly reported, and the preparation and evaluation of three skin-test antigens from material obtained from 3 of these patients is described.

One hundred and twenty subjects were tested. They comprised five groups, including patients with nonbacterial regional lymphadenitis, their family members and, as controls, "normal" family members. Also tested were a group of animal-hospital workers and, as controls, a group of employees of a large general hospital. Positive intradermal tests were elicited in 10 per cent of subjects who had no past or present history of the disease. Somewhat larger numbers of positive reactions were encountered among "high-risk" groups — animal-hospital personnel and members of families of patients — than among "low-risk" groups.

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A COMPARISON OF THE EFFICACY OF TETRACYCLINE AND PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA*

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TETRACYCLINE is a new broad-spectrum antibiotic derived from the catalytic dehydrogenation of chlortetracycline.[1,2] Chemically, it is similar to its analogues chlortetracycline and oxytetracycline, the only difference being that chlortetracycline has an additional chloride radical and oxytetracycline an additional hydroxyl radical. Preliminary studies by Finland et al.[3] have indicated that this antibiotic is effective in the treatment of pneumococcal pneumonia and other bacterial infections and that its toxicity is low. These encouraging results were considered to deserve extension and confirmation. This study of the comparative efficacy of tetracycline and penicillin in the treatment of alternate cases of pneumococcal pneumonia was therefore undertaken.

Methods

The study comprised all patients with the diagnosis of pneumococcal pneumonia who were admitted to the Medical Service of Firmin Desloge Hospital and Unit II, St. Louis City Hospital, during the period December 1, 1953, to July 15, 1954. Studies carried out on admission included x-ray examination of the chest, white-cell count, blood culture and inspection of the sputum by direct smear, quellung reaction, culture and mouse inoculation. Within twenty-four hours of admission, the following additional laboratory data were obtained: fasting blood sugar, blood nonprotein nitrogen or blood urea nitrogen and serum bilirubin. The assessment of the severity of illness on admission was based on the historical, physical and laboratory findings listed in Table 1, together with the clinical impression of the attending physician.

The patients were divided into two comparable groups, one receiving tetracycline‖ by mouth, and the other penicillin by intermittent intramuscular injec-

Table 1. *Analysis of Clinical Data.*

Datum	Patients Given Tetracycline		Patients Given Penicillin		Totals	Averages
	no.	percentage	no.	percentage	no.	percentage
Total patients	26	100.0	31	100.0	57	100.0
Male	19	73.0	19	61.3	38	66.7
Female	7	27.0	12	38.7	19	33.3
Patient under 40 yr. of age	5	19.2	6	19.4	11	19.2
Patient 40-59 yr. of age	9	34.5	9	29.0	18	31.6
Patient 60 yr. & over	12	46.3	16	51.6	28	49.2
Mild disease	6	23.1	8	25.8	14	24.6
Moderate disease	10	38.4	13	41.8	23	40.4
Severe disease	10	38.4	10	32.4	20	36.0
Duration of illness before therapy:						
1 or 2 days	11	42.3	17	54.7	28	49.2
3 or 4 days	6	23.1	7	22.6	13	22.8
5 or 6 days	2	7.7	2	6.5	4	7.0
Over 6 days	3	11.5	3	9.7	6	10.5
Indeterminate	4	15.4	2	6.5	6	10.5
Indications of severity:						
Bacteremia	6	23.1	6	19.4	12	21.0
Multilobar involvement	9	34.6	9	29.0	18	31.6
White-cell count <5000	0	0.0	1	3.3	1	1.6
White-cell count 5000-10,000	3	11.5	3	9.7	6	10.5
Shock	2	7.7	0	0.0	2	3.5
Disorientation	3	11.5	2	6.5	5	8.8
Jaundice	2	7.7	3	9.7	5	8.8
Alcoholism	7	27.0	5	16.1	12	21.0
Other complicating disease*	12	46.2	14	45.2	26	45.6
Pneumococcal type:						
1-8	18	69.2	20	64.6	38	66.6
Higher type	6	23.1	8	25.8	14	24.6
Untyped	2	7.7	3	9.7	5	8.8
Patient receiving prior treatment	1	3.9	1	3.2	2	3.5

*Significant cardiac, renal or liver disease, diabetes, bronchiectasis or emphysema.

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‖The tetracycline (as Achromycin), penicillin and some of the pneumococcus typing serum used in this study were kindly supplied by Lederle Laboratories Division, American Cyanamid Company through the courtesy of Dr. Stanton M. Hardy.

tion. All patients whose history number ended in an odd integer received tetracycline, and all whose history number ended in an even integer received penicillin. The dosage of tetracycline was 1 gm. on admission and 1 gm. every six hours thereafter. Crystalline potassium penicillin G in aqueous solution was given in dosages of 300,000 units at the time of admission and every twelve hours thereafter. Both other pulmonary diseases that could be confused with pneumococcal pneumonia.

Three patients were eliminated from the study for various reasons. One was given penicillin instead of tetracycline because of concomitant untreated latent syphilis. In 2 cases tetracycline was discontinued and penicillin substituted by personnel unfamiliar with the study, although a satisfactory response to tetra-

TABLE 2. *Results of Treatment.*

DATUM	PATIENTS GIVEN TETRACYCLINE		PATIENTS GIVEN PENICILLIN		TOTALS	AVERAGES
	NO.	PERCENTAGE	NO.	PERCENTAGE	NO.	PERCENTAGE
Total patients:	26	100.0	31	100.0	57	100.0
Duration of fever from start of therapy*:						
1 day	8	30.8	10	32.3	18	31.6
2 days	3	11.5	4	12.9	7	12.3
3 days	4	15.4	5	16.1	9	15.8
4-5 days	1	3.8	5	16.1	6	10.5
6-10 days	3	11.5	2	6.5	5	8.8
Over 10 days	4	15.4	3	9.7	7	12.3
Duration of white-cell count over 10,000*:						
1 day	6	23.1	8	25.7	14	24.6
2 days	4	15.4	4	12.9	8	14.0
3 days	3	11.5	3	9.7	6	10.5
4 days	4	15.4	2	6.5	6	10.5
5-10 days	4	15.4	7	22.6	11	19.3
Over 10 days	2	7.7	6	19.4	8	14.0
Duration of consolidation*:						
0-5 days	3	11.5	1	3.2	2	3.5
6-10 days	4	15.4	6	19.4	10	17.5
11-15 days	7	26.9	5	16.1	12	21.0
16-20 days	1	3.8	4	12.9	5	8.8
21-25 days	1	3.8	1	3.2	2	3.5
26-30 days	2	7.7	1	3.2	3	5.3
Over 30 days	6	23.1	8	25.7	14	24.6
Indeterminate	1	3.8	3	9.7	4	7.0
Complications:						
Sterile effusion	3	11.5	2	6.5	5	8.8
Atelectasis	1	3.8	2	6.5	3	5.3
Empyema†	1	3.8	0	0.0	1	1.8
Abscess‡	1	3.8	0	0.0	1	1.8
Spread§	1	3.8	1	3.2	2	3.5
Deaths	3	11.5	2	6.5	5	8.8

*Fatal cases not included.

†Fatal Case 3.

‡Fatal Case 4.

§X-ray evidence of spread of pneumonia to previously uninvolved lobe after beginning of therapy.

treatment schedules were continued until the temperature by rectum was 100°F., or below for at least forty-eight hours.

During the course of illness the following observations were made: temperature by rectum, every four hours; white-cell count daily until normal and then twice weekly, measurement of the hematocrit on admission and then twice weekly; and x-ray study of the chest before discharge and when otherwise indicated.

All patients who were admitted with the diagnosis of bacterial pneumonia were initially included in this study. Those in whom the diagnosis of pneumococcal pneumonia could not be substantiated were subsequently excluded. The criteria for the diagnosis of pneumococcal pneumonia were satisfactory clinical evidence of the disease in addition to roentgenographic evidence of pneumonia, the presence of pneumococci in the sputum or blood and the absence of cycline had occurred. These 3 patients recovered satisfactorily.

RESULTS

Comparability of Two Treatment Groups

Fifty-seven patients were included in the study, of whom 26 were in the tetracycline and 31 in the penicillin treatment group. Table 1 compares the clinical features of the disease manifested by the patients in the two groups at the time of institution of therapy, with particular reference to factors indicating the degree of severity of the infection. It is evident that the two groups are similar, and it is therefore valid to employ them in such a comparative study. It is further evident that there was a large proportion of moderately and severely ill patients in both treatment groups and hence that this study represented a rigorous test of tetracycline.

Results of Therapy

No differences in the therapeutic response to tetracycline and penicillin were noted (Table 2). The duration of fever, leukocytosis and consolidation after the beginning of therapy was similar in the two groups. There was no significant difference in mortality or frequency of complications. The pertinent features of the fatal cases are summarized below.

Toxicity

There were no side reactions in the 31 patients treated with penicillin. However, 8 of the 26 patients treated with tetracycline had untoward reactions (Table 3). In 4 of these patients anorexia, nausea, vomiting and diarrhea developed. Stool cultures showed a pure or predominant growth of *Staph. aureus* in each case. The data in these cases are outlined in Table 4. Three additional patients had which *Staph. aureus and Ps. aeruginosa* were cultured. These findings developed on the sixth day of therapy and persisted for three days despite immediate cessation of the drug. In another case a nonpruritic, macular, erythematous eruption appeared on the trunk and extremities on the sixth day of therapy and continued for five days, despite the fact that tetracycline was stopped on the day that it appeared; the patient was on no other drug that might have caused the rash.

Infections due to tetracycline-resistant gram-negative rods complicated the therapy of 2 patients. The first of these was a lung abscess associated with a heavy pure culture of proteus that appeared in fatal Case 4. The second superinfection occurred in a fifty-one-year-old alcoholic man who had an unsuccessful lumbar puncture on the fourth day of tetracycline therapy because of a history of treated, latent syphilis. On the next day, severe pain developed at the site of the lumbar puncture. Subsequently, a diagnosis of epidural granuloma and vertebral osteomyelitis due to *Ps. aeruginosa* was established by surgical exploration. Although these 2 infections cannot be considered definite sequelae of tetracycline therapy, the association is worth noting. No such infections occurred in the penicillin-treated series.

TABLE 3. *Untoward Reactions in 26 Patients with Pneumococcal Pneumonia Treated with Tetracycline.*

REACTION	NO. OF CASES
Nausea, vomiting & diarrhea with *Staphylococcus aureus* predominant organism in stool culture	4 (15.4%)
Glossitis & pharyngitis associated with *Staph. aureus & Pseudomonas aeruginosa*	1 (3.8%)
Maculopapular erythematous eruption	1 (3.8%)
Superinfection:	
Lung abscess due to proteus	1 (3.8%)
Vertebral osteomyelitis due to *Ps. aeruginosa*	1 (3.8%)
Total	8 (30.8%)

SUMMARY OF FATAL CASES

J. S., a 61-year-old alcoholic man with severe cirrhosis of the liver, entered the hospital with pneumonia of the left upper lobe and bacteremia due to *Diplococcus pneumoniae*, Type 1. His course was complicated by delirium tremens and jaundice, and he died suddenly on the 7th day of penicillin therapy. No autopsy was done.

TABLE 4. *Clinical Data in 4 Cases of Diarrhea Associated with Tetracycline Therapy.*

CASE NO.	DURATION OF THERAPY BEFORE ONSET OF DIARRHEA	NO. OF STOOLS PER DAY	TOTAL DURATION OF DIARRHEA	DURATION OF DIARRHEA AFTER DISCONTINUANCE OF TETRACYCLINE	DRUG SUBSTITUTED FOR TETRACYCLINE	*Staph. aureus* IN STOOLS	NAUSEA & VOMITING
	days		*days*	*days*			
1	6	(Many)	2	1	Penicillin & erythromycin	Pure culture	Yes
2	3	10-20	10	6	Penicillin	Predominating	Yes
3	1	15-20	3	2	Penicillin	Predominating	Yes
4	4	(Many)	4	3	Penicillin	Predominating	Yes

moderate diarrhea during the administration of tetracycline — in each case in association with the presence of staphylococci in the stools. One of these patients had uremia as another potential cause of the diarrhea. The diarrhea in the other 2 cases subsided spontaneously despite the continuation of tetracycline therapy. These cases, which are considered to represent possible but not definite evidence of toxicity, are not included in Tables 3 and 4.

The tongue and throat of 1 patient became red and sore and covered with a white exudate from

E. T., an 87-year-old woman, was admitted to the hospital with pneumonia of the left upper lobe and bacteremia due to *D. pneumoniae*, Type 1. Her course was characterized by progressive jaundice, paralytic ileus and deterioration. She died in shock on the 7th day of penicillin therapy. No autopsy was done.

C. R., an 82-year-old man with chronic emphysema, had pneumonia of the right middle and lower and left lower lobes and bacteremia due to *D. pneumoniae*, Type 1. His course was complicated by the appearance of bilateral empyema. He died in shock after 32 hours of tetracycline therapy. Autopsy confirmed the findings mentioned above.

C. S., a 48-year-old alcoholic man, entered the hospital

with pneumonia of the right and left lower lobes and bacteremia due to *D. pneumoniae*, Type 7. After an initial favorable response to tetracycline an abscess appeared in the left lower lobe on the 5th day of therapy, together with evidence of spread to the left upper lobe. Sputum smear and culture revealed a heavy growth of proteus that was resistant to tetracycline but sensitive to streptomycin and chloramphenicol. Treatment was begun with those antibiotics, but the subsequent course was characterized by progressive deterioration, delirium tremens and a large pyopneumothorax on the left. He died on the 8th day of therapy. Autopsy confirmed the findings mentioned above and, in addition, disclosed an abscess, 3 cm. in diameter, in the right lower lobe.

M. J., a 76-year-old man with arteriosclerotic heart disease and congestive heart failure, and with a tabetic bladder, chronic pyelonephritis associated with *Ps. aeruginosa* and uremia (blood urea nitrogen of 76 mg. per 100 cc.), entered the hospital with pneumonia of the right lower lobe due to *D. pneumoniae*, Type 3, and mild shock. He responded to tetracycline therapy for the first 2 or 3 days, but on the 4th day of therapy the temperature again rose. He had 1 or 2 loose stools on the 1st day of therapy and 3 or 4 stools yielding a moderate growth of staphylococcus on the 5th. He died on the 6th day with a serum potassium of 8.1 milliequiv. per liter. No autopsy was done.

Discussion

Previous reports[4-7] have emphasized the fact that the place of a new chemotherapeutic agent in the treatment of a specific infection for which useful remedies are already available is one that can best be determined by comparative study. To be acceptable such a new agent should be equally effective in terminating infection and no more toxic than drugs currently in use. Tetracycline, in the relatively high dosage of 4 gm. a day by mouth, was apparently as effective in terminating infection as penicillin, but considerably more toxic in this small group of patients with pneumococcal pneumonia.

There is ample evidence (Table 1) that a number of the patients included in this study had severe pneumococcal pneumonia with such unfavorable prognostic signs as advanced age, bacteremia, multilobar involvement and major concomitant disease. It is important to emphasize that tetracycline could not be shown to be less efficacious than penicillin in terminating infection in these severe cases of pneumococcal pneumonia.

However, though tetracycline at this dosage level proved as effective as penicillin, its use was associated with frequent unfavorable side reactions. The most common untoward symptom complex was nausea, vomiting and diarrhea associated with a predominant growth of *Staph. aureus* in the stool culture. There is ample evidence that such a diarrhea is a common, distressing and sometimes fatal complication of therapy with other analogues of tetracycline.[3,8] It is essential, therefore, to know whether the prevalence of this complication is influenced by the dosage level or the analogue of tetracycline used. Finland et al.[3,8] have demonstrated that with oxytetracycline, chlortetracycline and tetracycline the frequency of diarrhea varies directly with the dosage. With tetracycline therapy they described diarrhea in 2 per cent of 51 patients receiving 1 to 1.2 gm. and in 5 per cent of 59 receiving 2 gm. a day. The present study demonstrates a 15 per cent prevalence of diarrhea in 26 patients receiving 4 gm. a day. Finland and his associates[8] have shown by comparative study that at a given dosage diarrhea is more frequent with oxytetracycline than with chlortetracycline therapy. There is some indication that diarrhea is less common with tetracycline than with chlortetracycline therapy,[3] but a direct comparative study is still needed to make this evidence conclusive. No conclusions in this regard can be drawn from the study reported in this paper.

Summary

A comparative study of the efficacy of tetracycline given by mouth in a dosage of 4 gm. a day and of parenteral administration of aqueous potassium penicillin G in a dosage of 600,000 units a day in the treatment of pneumococcal pneumonia is described. Fifty-seven patients were studied, many of whom had severe pneumonia. No differences in the therapeutic responses to the two drugs could be demonstrated. The use of tetracycline was complicated by a significant prevalence of untoward reactions. There were 4 cases of diarrhea associated with staphylococci.

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MEDICAL PROGRESS

CLINICAL PULMONARY PHYSIOLOGY

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THE most significant progress in the field of pulmonary physiology has been a reawakened interest in clinical application. The ever-increasing attention devoted to evaluation of pulmonary function in man has been prompted by the great advances in specific medical therapy and safer, more effective surgical treatment of pulmonary disease. The growing complexities of anesthesia have called for more objective evaluation of the cardiovascular and respiratory systems, and the expanding field of cardiac surgery not only has stimulated clinical investigation of cardiovascular function but also has called for a better definition of the extent of pulmonary, as opposed to cardiac, damage. An increasing awareness of industrial respiratory hazards, wider application of workmen's compensation laws and the greatly expanded responsibilities of the armed forces and Veterans Administration in this regard have led to a greater number of requests for objective evaluation of pulmonary disability.

The emergence of the laboratory of clinical pulmonary physiology from a few research units and isolated sanatoriums to clinical centers throughout the world has had three important consequences.

In the first place most of the recent contributions to knowledge in pulmonary physiology have come from the clinical laboratory. Significant developments in methodology include the demonstration of inadequacy of static lung-volume tests and greater use of dynamic ventilation measurements, more accurate measurements of physiologic dead space and intrapulmonary gas distribution by single-breath tests, a change of emphasis from expressions of external ventilation to alveolar ventilation and from expressions of blood gas content to gas tensions, the revival and modification of gas-bubble and carbon monoxide methods for measurement of gas diffusion and improved technics for determination of differential function. The concepts of uneven alveolar ventilation, the demonstration of local regulation of pulmonary circulation by local changes in gaseous environment, the determination of the alveolar-arterial oxygen "gradient," the differentiation between the factors of venous admixture and pulmonary membrane responsible for this gradient and calculation of diffusion coefficients, detailed analysis of the mechanics of breathing and of physiologic changes at altitudes, and during positive pressure and resistance breathing, have all originated or have been expanded and amplified in the clinical laboratory.

A second development has been a better understanding of certain pathologic processes. Arbitrarily chosen examples are the clinical recognition of respiratory acidosis and carbon dioxide narcosis not only in chronic pulmonary disease but also during anesthesia and artificial respiratory maneuvers, the clarification of the nature of incapacity produced by bronchial asthma, pulmonary emphysema, pneumothorax and paradoxical chest-wall motion and, perhaps most important, the development of the concept of alveolar-capillary block.

The third result of the resurgent interest in clinical pulmonary physiology comprises a number of therapeutic developments and a changing emphasis in the management of certain pulmonary diseases. In thoracic surgery preservation of function by small segmental and wedge operations, by lesser and more selective rib resections and by freer use of plombs, restoration of function by pulmonary decortication, breathing exercises and preservation of phrenic-nerve integrity have been encouraged by results of pulmonary-function studies. In internal medicine the freer use of oxygen in patients with diffusion difficulties and the greater care with oxygen in others with chronic respiratory acidosis, abandonment of therapeutic pneumothorax, prompt aspiration of pleural effusions, recognition of hypoventilation and increasing emphasis on improving ventilation by more liberal use of pneumoperitoneum, emphysema belts, breathing re-education, intermittent positive pressure breathing and respirators may be mentioned.

This review was written primarily to summarize recent advances in pulmonary physiology that have come from the clinical laboratory. Certain older principles and methods are restated to provide a suitable background. Presently accepted methods are critically examined, and their interpretation and limitations emphasized. Application of this study in the clinical management of the patient is suggested.

This review is not intended as a summary of the entire field or as a technical guide for performance of pulmonary-function studies. A number of reports that have appeared within recent years have defined pulmonary function, standardized methods, presented normal values, revised nomenclature and described technics.[1-10]

For correct evaluation of the laboratory results certain limitation of the data must be appreciated. In many tests "normal" performance has not been well established. Often, reported figures are based on too

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small a sample to be significant. Particularly for ventilatory studies "normal" values derived from a large population have a standard error of about 20 per cent or more.[2,3,6] Accordingly, in an individual case, a result of 80 per cent of "predicted" may mean normal performance or may represent a 40 per cent impairment. This uncertainty is important in legal medicine.[11,12] Because of these large variations, pulmonary-function studies are not useful for detection of minor functional impairment.[6] Finally, it must be emphasized that physiologic tests alone do not permit a pathological diagnosis and, with the exception of bronchospirometry, do not indicate anatomic location.

Classification of Pulmonary Function

Analysis of pulmonary function is facilitated by subdivision of the physical events of respiration. The term *ventilation* is often used to define the mass displacement of air between the outside atmosphere and the interior of the lungs. *Respiratory gas exchange* refers to the diffusion of gases across the alveolar-capillary membrane.[2] An intermediary step, the *distribution* or *mixing* of inhaled air within the lungs, is considered as part of ventilation by some[6] and is included with respiratory gas exchange by others.[2] Clinically, defects of these successive events usually do not appear singly. However, an orderly analysis of pulmonary function is possible only if one is constantly aware of the particular defect that an examining procedure is designed to explore. Certain analytical procedures[13] are affected by so many nonrelated factors that conclusions concerning the type or even the presence of pulmonary insufficiency are not justified.

Ventilatory Insufficiency

Clinicians are more concerned with ventilation than with other aspects of pulmonary function because ventilatory insufficiency is far more common than defective distribution or gas exchange, ventilatory insufficiency occurs quite commonly alone whereas major distribution or diffusion defects are usually accompanied by some ventilatory defect as well and the adequacy of ventilation can be measured rapidly and with relative accuracy by means of simple instruments whereas assessment of distribution and diffusion requires elaborate analytical procedures and is less reliable. Physiologic activity of a system is usually quantitated in terms of performance *per unit of time*. Ventilatory capacity should also be expressed in these terms because it represents the volume of gas that can be made available for exchange with the pulmonary arterial blood, whose flow is again measured in terms of volume per unit of time. A vital capacity of 4000 cc. that requires ten seconds for delivery may carry more serious implications than one of 1000 cc. that can be exhaled in one second.

The simple concept of the thoracic cage and diaphragm as a pair of bellows has been helpful in the definition of ventilatory insufficiency. A cylinder with a large outlet at one end and with a piston and long arm can be imagined as a mechanical analogue. The air displaced as the piston moves from one end of the cylinder to the other corresponds to maximal stroke volume or vital capacity. One can diminish this stroke volume by reducing the range of motion of the piston arm. Clinically, this occurs when the respiratory musculature is weakened as in poliomyelitis, myasthenia gravis or phrenic-nerve paralysis. The maximal stroke volume can also be reduced by the insertion of a stop in the cylinder wall, preventing full range of motion of the piston. This occurs whenever the amount of aerated parenchymal lung tissue is diminished. Extrapleural compression by effusion or pneumothorax, bronchial occlusion with atelectasis, actual loss of tissue caused by excision or replacement by tumor and reduced alveolar space due to pulmonary capillary engorgement may all be responsible for this situation. This type of impairment has been referred to as *restrictive ventilatory insufficiency*,[2] and the degree of impairment is faithfully reflected by diminution of the vital capacity.

Another type of defect, *obstructive ventilatory insufficiency*,[2] is encountered more often. With the mechanical model, this impairment can be produced by a reduction in the size of the cylinder outlet. The piston can still move its full range, but more time is required to force the air through the narrow opening. Partial occlusion of major airways — for instance, by tumor — may cause this defect. Diffuse obstruction results if the diameter of the smallest air passages is narrowed by spasm or edema.

In the previous illustration the cylinder contained only air, and no forces other than the respiratory muscles acted on the piston. Actually, the piston is being constantly pulled inward by the elastic fibers of the lung. Interruption of many of these fibers causes the piston to move to a more inspiratory position (barrel chest), and, more important, the piston meets the resistance of the less collapsible lung and motion is again slowed. Disruption of the pulmonary architecture contributes to the obstructive ventilatory insufficiency in pulmonary emphysema.

In obstructive defects the ventilatory capacity is reduced primarily because the number of stroke volumes exchanged per unit of time — the revolutions per minute of an engine — is smaller. If one ignores the dimension of time by measuring only the maximal stroke volume (vital capacity) an erroneous impression of the degree of ventilatory insufficiency is obtained. These considerations are borne out by clinical experience: the vital capacity correlates well with dyspnea in patients with restrictive insufficiency; there is no such correlation in patients with obstructive defects.[2,6,14-16] A restrictive defect is not disabling unless it is severe because the decrease in maximal ventilation is roughly proportional to the loss of

aerated tissue. In contrast, air-flow obstruction of even minor degree may seriously reduce maximal ventilatory capacity because resistance to flow increases in inverse proportion to the fourth or fifth power of the internal diameter of the tube.[17,18]

Spirometry

Two methods are commonly employed for the measurement of resting and exercise ventilation, gas exchange and lung volumes. The first or *closed-circuit* technic is well known to those acquainted with instruments for determination of the basal metabolic rate. Rebreathing of gas from a small recording spirometer with carbon dioxide absorption by soda lime entails certain analytical advantages not provided by any other method. Graphic recording and immediate visualization of respiratory excursions permit direct reading of tidal volumes, respiratory rate, lung volumes and maximal breathing capacity; irregular breathing, sudden changes in the pulmonary resting position and technical difficulties are noted during the test; a permanent record is available for later analysis of breathing pattern; direct recording of oxygen uptake obviates the necessity for later gas analysis; the method is also suitable for foreign-gas equilibration studies. Of the three commonly used instruments the Benedict–Roth apparatus[19] is best known in this country. It is semiportable, well standardized and easily modified for special investigations. A ventilograph attachment[20] avoids tedious additions for calculation of minute ventilation. The expired carbon dioxide is absorbed by soda lime and cannot be measured. With the usual fishmouth valves and ventilograph there is considerable resistance to breathing. In the Knipping[21] spirometer the expired carbon dioxide can be measured by bubbling the expired air through an alkaline solution and by later liberation of the gas by addition of acid. Resistance breathing is eliminated by air circulation with a motor-driven fan. The Krogh[22] spirometer has a wedge-shaped container that is pivoted on knife blades and floats in a water-filled box. The entering gas swings the box upward in an arc, and a weight is used for perfect counterbalance. This spirometer offers less resistance and inertia than the other two designs.

Certain problems of the closed-system rebreathing apparatus can be solved by relatively simple modification. Devices for direct measurements of minute ventilation and carbon dioxide elimination have been mentioned. Other difficulties such as spirometer inertia[23] and a degree of resistance breathing[24] cannot be avoided. The most serious problem is the constantly changing composition and initial high oxygen tension of the inspired gas because the spirometer must be filled initially with a high concentration of oxygen to prevent later anoxia as oxygen is removed from the system. A number of manual and automatic devices have been designed to facilitate constant breathing of room air. Oxygen is added to the system at the rate at which it is removed, but with the simpler of these methods oxygen uptake cannot be measured[25,26] and the more elaborate systems are not suitable for clinical use.[27-29] In the drum-balloon systems of recent popularity the inspired and expired gases are separated by a rubber balloon, and the spirometer is merely used to reflect volume changes within the drum.[30-34] Problems of size and temperature control have been discussed.[34]

In the *open-circuit* method room air or a prepared gas from a tank is inhaled through one valve and exhaled through another into a rubber bag or second tank. The advantages of this method, in addition to constant room-air breathing, are more accurate determination of gas exchange, unlimited duration and intensity of exercise, adequate portability, avoidance of spirometer-inertia errors and the possibility of measuring foreign-gas clearance. Only average ventilation for a given period can be ascertained by this method, and gas analyses are required for calculation of oxygen uptake and carbon dioxide elimination. Gas permeability of the usual Douglas-type bags may lead to inaccuracies.[35] Less permeable, much lighter and very inexpensive meteorologic neoprene balloons are now often used for collection of expired gas.

The choice of apparatus is dictated by conditions of study, the determination that is of greatest interest and the type of patient to be examined. In general, the Benedict–Roth instrument is most suitable for clinical and routine studies, and the open-circuit method has been largely confined to research laboratories. Size, expense and required calculations make these systems unsuitable for routine ventilation recording during administration of anesthesia or artificial respiration and for large-scale surveys. Small ventilation meters have been developed for these special situations.[36] A more detailed analysis of open-circuit and closed-circuit spirometry is available.[24]

Lung Volumes

Definitions

A nomenclature for the subdivisions of the lung volume agreed upon recently[5] is now generally accepted. The *vital capacity* is the greatest volume of gas that can be expelled by voluntary effort after maximal inspiration; it is subdivided into the *inspiratory capacity,* the maximal volume that can be inspired from the end-expiratory position, and the *expiratory reserve,* the maximal volume that can be exhaled from the end-expiratory position. The *functional residual capacity* is the volume remaining in the lungs at the end of a quiet expiration; it is composed of expiratory reserve and the *residual volume,* the volume of gas remaining in the lungs after forced expiration. The *total lung capacity* is the sum of the vital capacity and the residual volume.

Vital Capacity

During the nineteenth century clinical evaluation of

pulmonary function was generally limited to measurement of the vital capacity, and this tradition still persists in many places. Hutchinson[37] first explored the clinical significance of this volume, and, although he "advanced deductions with modesty and hesitation," little has been added to his observations during the past hundred and eight years. Figure 1 reproduces his conception of an apparatus for the measurement of vital capacity. He found a larger vital capacity in males than in females, and in tall than in short subjects. He noted that the volume decreased

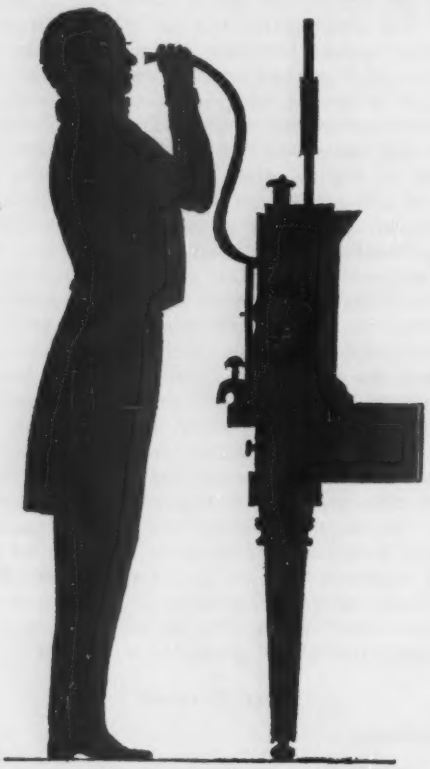

FIGURE 1. *Apparatus for Measurement of Vital Capacity (Reproduced from Hutchinson[37]).*

with age and that the vital capacity of "common labourers is larger than that of ladies and gentlemen." His findings of a close relation between dyspnea and reduction of vital capacity are often quoted; forgotten are his experiences with a patient who lacked "expiratory power," had difficulty in breathing and yet had a normal vital capacity. Subsequent failure to realize the limitations of the test has caused much faulty interpretation of respiratory complaints.

The simplicity and rapidity of the procedure has led to an abundance of "normal standard tables" and formulas for prediction. The limitations of these formulas apply not only to the vital capacity but to most other ventilatory-function tests. The volume varies not only with sex, age, height or body surface — variables that can be incorporated in regression equations — but also with less tangible factors such as muscular development, occupation and stature. Therefore, the standard errors are large, and small deviations from the normal cannot be detected. Secondly, an inadequate number, age range or type of normal subjects has been used for derivation of formulas and tables. A great need exists for the uninspiring task of obtaining statistically significant normal values for clinical ventilatory tests. For prediction of the vital capacity of adults the regression equations of Baldwin, Cournand and Richards[2] are often used whereas for children the normal standards of Stewart[38] seem to be generally accepted.

The training factor is negligible in the vital-capacity test. In a triplicate examination of 1000 patients the first effort averaged 97 per cent of the last or best effort.[39] Daily variations are as little as 2 per cent[40] except in patients with bronchial asthma[14] and those who fail to comprehend or to co-operate. The vital capacity is decreased by about 5 per cent in the supine position, most probably because of the greater thoracic and lung blood volume, and the higher position of the diaphragm.[37,41-43] Maneuvers that decrease the amount of blood in the chest—for example, application of tourniquets,[44] venesection,[45] administration of peripheral vasodilators,[46,47] the Valsalva maneuver[48] and positive pressure breathing[47] — all cause a slight increase in the vital capacity.

For evaluation of pulmonary function it is preferable to rely on history, physical examination and fluoroscopic observation than on measurement of the vital capacity as the only test of function. Reduction of the vital capacity indicates a restrictive defect without excluding complicating obstruction. The test is helpful for following the course of restricting disease: changes in aeration due to pleural effusion, pulmonary edema or stages of collapse therapy are reflected faithfully by changes in the vital capacity. The test is most useful for comparison and correlation with other tests of ventilatory function.

Inspiratory Capacity and Expiratory Reserve Volume

These reflect the state of inflation of the lungs or the "pulmonary resting position" at the end of quiet expiration. The expiratory reserve is normally 20 to 25 per cent of the vital capacity. In certain situations, as during airway obstruction, breathing occurs with a more inflated chest; the expiratory reserve increases at the expense of the inspiratory capacity without change in the vital or total lung capacity.[18,24,49,50] The opposite occurs when the diaphragm ascends as when the subject assumes the supine position,[41-43] in pregnancy[51,52] and during artificial pneumoperitoneum treatment.[53-55] Breathing with relatively deflated lungs is of interest in the therapy of tuberculosis because it signifies a degree of "collapse."[51-57]

Clinically, an increased expiratory reserve volume

suggests hyperinflation due to obstruction without damage of pulmonary elastic structures; on effort the lungs can still be deflated to a normal residual volume. In restrictive defects both vital-capacity components are reduced, and, later, the expiratory reserve may disappear.

The inspiratory capacity and expiratory reserve can be recorded separately. The volume obtained by addition of these two components is termed "combined" vital capacity. In contrast, maximal inspiration immediately followed by forceful expiration gives the "actual" vital capacity. These two volumes are identical in normal persons and in patients with restrictive defects. Long-standing obstruction and altered lung structures, as in asthma or emphysema, lead to "air trapping" and inability to move the thoracic cage and diaphragm from fullest inspiration to maximal expiration in a single motion. In such cases the "combined" vital capacity may be as much as 1000 cc. larger than the "actual" vital capacity.[58,59] This discrepancy has been made the basis of a modified vital capacity test.[60]

Residual Volume

Residual volume, or the gas remaining in the lungs at the end of forced expiration, must be measured by indirect methods. Radiologic measurements take little time and are suitable for large-scale surveys. In normal subjects they permit some measure of total lung capacity; in patients with pulmonary disease correlation with more exact methods has generally been poor[61-63] although certain recent changes in measurement have given better results.[64] Physical methods making use of explosive decompression have shown promise[65,66] but are not suitable for clinical use because of the required pressure chamber.

All other technics make use of foreign-gas mixtures and can be divided into two groups. The *closed-circuit method* requires rebreathing from a bag or small spirometer, which initially contains a known volume and concentration of hydrogen,[56,67,68] oxygen[58,69] or helium.[63] After a few breaths[69] or several minutes[58] it is assumed that complete mixing of spirometer and lung gases has occurred. Modifications permitting observation of the mixing process by continuous or terminal gas analysis have been described.[70,71] The residual volume can be calculated from the known initial and final volume and gas concentration in the spirometer.

In the *open-circuit technic* pure oxygen is breathed, usually for seven minutes.[72] The exhaled gas is collected, and its volume and nitrogen content measured. Since the lungs initially contained 80 to 81 per cent nitrogen, the volume of gas in the lungs at the time oxygen breathing was started can be calculated. A common criticism — that the respiratory level is not known when oxygen breathing is started — can be overcome by use of a drum-balloon system[32,33] permitting room-air breathing and simultaneous spirographic recording.[34] With painstaking technic, airtight systems and accurate chemical or physical gas analysis, duplicate determinations should check within 5 per cent.[2,3,40,52] Results are less reliable when the residual volume is very large because trapping and uneven distribution of gases interfere with mixing.[72] The closed-circuit method is somewhat more rapid but requires electronic gas analysis. The more elaborate open-circuit technic, with certain modifications, gives the most accurate results.[72]

Much importance has been attached to the percentage of the total lung capacity occupied by residual volume — the so-called R.V.-T.L.C. ratio. This is normally no more than 20 to 30 per cent.[41,56,62,73] Although ratios of 40 and even 50 per cent have been recorded in apparently healthy elderly subjects[74] a ratio of more than 35 per cent is often considered diagnostic of pulmonary emphysema.[75] Furthermore, the severity of emphysema has been classified on the basis of this ratio[76] and has been used for calculation of a "ventilation factor."[12] Classifications on this basis neglect the fact that the R.V.-T.L.C. ratio can also be elevated because of a decrease in the denominator, the total lung capacity, which is commonly reduced with pain, dyspnea, muscular weakness or chest binders and previous operations hindering fullest inspiration.[6,77,78] Therefore, an elevated ratio is not necessarily indicative of emphysema although in emphysema the ratio is invariably elevated.[6,15,58,72,76,79]

Functional Residual Capacity

This is the most significant subdivision of the lung volume and the only volume that can be measured without active participation by the patient. Volumes varying by no more than ± 75 cc. have been recorded for the same patients on more than twenty occasions over the course of six years.[72,77]

An increased functional residual capacity may be due to emphysema or "hyperinflation." I prefer to think that the increase is due to structural emphysema if the residual volume is proportionately enlarged whereas breathing with an excessively inflated lung signifies reversible hyperinflation if, on maximal expiratory effort, the lungs can be reduced to a normal minimal size.[77] Hyperinflation is common with obstruction of major bronchi and is typical in bronchial asthma of recent origin, external resistance breathing[18,49,50] and positive pressure breathing.[50] Local hyperinflation occurs after loss of lung tissue, as in apical tuberculosis of long standing[81-83] or after pulmonary resection,[6,77] a condition often termed "compensatory emphysema." Dyspnea out of proportion to the loss of lung tissue suggests that emphysema may have developed, and this is often confirmed at post-mortem examination.[82,83] The functional residual capacity always increases during exercise.

Dynamic Ventilatory Studies

Maximal Breathing Capacity

With the maximal breathing capacity, Hermannsen[84] introduced a dynamic or time element into ventilatory-function tests. This capacity is defined as the maximal volume of air in liters that can be moved by voluntary effort during one minute. Any abnormality of the structures involved in ventilation, including the neuromusculature, bony thoracic cage, pleura, pulmonary parenchyma and airways, results in a reduction of this volume. Therefore, the maximal breathing capacity correlates more closely with the degree of dyspnea than any other test of ventilatory function.[2,14,39,76,85,86]

The expired air can be collected with a high-velocity directional valve and a Douglas bag,[85,86] or the volume can be recorded directly with a closed-circuit spirometer.[2] Tubing with large internal diameter and low-resistance valves is essential because the test is sensitive to airway obstruction.[86] Spirometer inertia, which is a problem in the closed-circuit method, may cause falsely large or unduly small results, depending on the phasing of spirometer-bell and water-column movements.[23] Patients are instructed to breathe as deeply and as rapidly as possible, and the exhaled air is collected for fifteen[2,6] to thirty[85,86] seconds; the longer period is preferable because the respiratory effort during exercise is simulated more closely. Demonstration of fatigue contributes to the diagnostic importance of the test: normal persons show no progressive diminution of ventilation during the first thirty seconds[86,87] whereas patients with limited cardiac output and some patients with obstructive ventilatory insufficiency may maintain a "best" effort for only a few seconds.[86] The "learning effect" is small, and reproducibility with 5 per cent is usual.[39,59,86,89]

In normal subjects this voluntary maximal hyperventilation results in a much larger minute volume than hyperventilation elicited by breathing gas mixtures containing carbon dioxide. It is also larger than the ventilatory requirement during maximal physical effort[84,90] because exercise tolerance is limited by cardiac output and muscle metabolism and not by ventilation.[87]

The maximal breathing capacity of normal women ranges from 50 to 120, and that of men from 60 to 170 liters per minute.[2] Individual variation is large, and standard errors from 12 to 23 per cent have been reported.[2,59,86,89,90] In addition to sex the volume correlates most closely with age[2,86] and to a lesser degree with body surface.[2,89] The regression equations of Baldwin, Cournand and Richards[2] are often used for prediction of normal values. For males the formula of Wright[86] is useful.

Air Velocity Index

The correlation between maximal breathing capacity and vital capacity is poor,[6,39,59] particularly in obstructive ventilatory insufficiency.[14,16] The maximal breathing capacity reflects maximal tidal volume as well as speed of exchange whereas the vital capacity reflects maximal tidal volume alone. One can gain additional information by comparing the results of the two tests. A ratio of number of liters of maximal breathing capacity per liter of vital capacity was mentioned in the older literature. Tuberculous patients with a low ratio proved to be poor surgical risks.[91] This "capacity ratio" averages 32.8 liters of maximal breathing capacity per liter of vital capacity in young normal subjects.[92] A low "capacity ratio" has been thought to suggest increased air-flow resistance or decreased muscular force.

The maximal breathing capacity decreases with age more rapidly than the vital capacity, the former being closely related to body surface and the latter correlating better with height. Therefore, I prefer to compare the two volumes, each expressed as percentage of the predicted normal value. The ratio of percentage of predicted maximal breathing capacity to percentage of predicted vital capacity is called "air velocity index."[93] In normal persons and in patients with restrictive insufficiency this index is 1.0 or larger whereas in patients with obstructive defects it is invariably less than 1.0. The index must be regarded in the light of absolute figures because an equal reduction of both volumes is not reflected by an abnormal air velocity index. Low indexes suggest a search for the cause of the "obstruction" by administration of bronchodilators, fluoroscopic observation, studies of residual volume and bronchoscopy.

Time Element in Vital Capacity

Hutchinson,[37] with his test for "respiratory power," and a number of investigators since have suggested that a delay in the time of forced expiration may indicate obstruction of air flow. Graphic recording of the vital capacity on a rapid kymograph permits measurement of the time required for maximal expiration. Slowed air flow, shown by a flattened spirographic slope, is an essential manifestation of pulmonary emphysema[58,60] and of bronchial asthma.[14,16] Histamine-induced bronchospasm may cause a change of the slope or speed of flow without a decrease of the total volume of air moved.[94] The rate of air flow may be so slow that the delivered volume is limited by the patient's breath-holding ability.[39,95]

Quantitative expressions of the time-volume relation have been suggested. Bruce[96] divided the vital capacity by the total expiratory time; the resulting "vital rate" ranged from 3 to 8 liters per second in normal persons. Tiffeneau and Pinelli[97] called the volume delivered during the first second of the effort the *capacité pulmonaire utilisable à l'effort*. By arbitrary multiplication of this volume by 30 an "indirect maximal ventilatory capacity" was obtained. The breathing capacity calculated in this manner does not correlate well with the actual maximal breathing

capacity.[7,98] Patients adapt the frequency of their breathing under stress to a rate best suited to their defective ventilatory mechanics. In restrictive defects the maximal tidal volume is exchanged more rapidly than normal, chiefly because the airways offer relatively less resistance to the smaller volume. In obstructive defects, on the contrary, a lower than normal frequency is chosen because during rapid breathing air is trapped, the functional residual capacity increases and the lungs are less easily deformed.[14,93,99] This frequency adjustment of patients with ventilatory insufficiency is one of the reasons why the test of maximal breathing capacity is superior to any indirectly calculated ventilatory capacity.

The time-volume relation can be measured from the spirogram. The volume exhaled during the first second[97,100] or during the first three seconds[12] of the maximal expiratory effort has been considered most significant. The complexities and expense of a low-resistance spirometer, multiple-speed kymograph, constant paper feed and tracing analysis can be avoided by a simple attachment to the ordinary, dial-type vital-capacity machine.[101,102] This records automatically the total vital capacity and the fraction of the total volume exhaled during the first, first two or first three seconds of the maximal expiratory effort. The onset of expiration automatically initiates the timing cycle. This instrument, because of its small size, simplicity and low cost is useful on the hospital ward and in the clinic. Normal persons are capable of exhaling 83, 94 and 97 per cent of the total vital capacity during one, two and three seconds.[10] With restrictive defects the total vital capacity is reduced, but the timed percentages remain normal. In the presence of airway obstruction or impaired pulmonary elastic recoil, small reductions of total vital capacity are accompanied by marked decreases of timed capacities. Unlike the vital capacity, the timed capacities correlate well with maximal breathing capacity, air velocity index and ratio of residual volume to total lung capacity.[101]

(To be continued)

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MEDICAL INTELLIGENCE

PROLONGED STAPHYLOCOCCEMIA*

Report of a Case

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THE course of staphylococcal septicemia is usually acute and fulminating, and, before the advent of antibiotics, the outcome was invariably fatal. With the introduction of antibiotics numerous cures were reported,[1] but since 1949, with the development of antibiotic resistance, staphylococcal infections have been more difficult to eradicate.[2,3] It is the purpose of this paper to report a case of staphylococcemia of over two years' duration.

CASE REPORT

A 23-year-old Negro was well until October, 1951, when, while in the Army in Japan, he had a perirectal abscess, which was incised and drained. He received no antibiotics at this time. Three weeks later he was readmitted to the hospital with fever, chills, epistaxis, cough, hemoptysis and jaundice. He also had some generalized muscular aches, weakness and a mild diarrhea. The temperature was 103.4°F., and the pulse 130; the blood pressure was 110/60. The patient was acutely ill. The scleras were icteric. The lungs were clear. The heart was not enlarged, but a harsh systolic murmur was heard at the apex. The liver was enlarged and tender. The spleen was not palpable, and petechiae were not seen. The white-cell count was 20,000, with a shift to the left, and the hemoglobin 13.5 gm. per 100 cc. Urinalysis revealed a ++++ test for albumin, with numerous red and white cells in the sediment. The blood urea nitrogen was 32 mg., and the bilirubin 4.5 mg. per 100 cc. Blood cultures were taken, and *Staphylococcus aureus* was grown out. The organism, which was also found in the urine and sputum, was resistant to penicillin, chlortetracycline and oxytetracycline, moderately sensitive to chloramphenicol and sensitive to streptomycin.

The initial therapy consisted of penicillin for 3 and streptomycin for 2 months. Later chlortetracycline was added for about 1 month. The patient ran a febrile course and required numerous transfusions for anemia. However, the icterus gradually cleared, and the blood urea nitrogen returned to normal although the albuminuria persisted. In January, 1952, thrombophlebitis developed in both legs but was successfully treated with Dicumarol. In February it was noted that the heart was enlarged, and a gallop rhythm was apparent. He was digitalized. Blood cultures during this period continued to be positive for *Staph. aureus*. In March, he was transferred to the Valley Forge General Hospital, where he was found to have an enlarged heart, a tachycardia, a soft systolic murmur at the third intercostal space to the left of the sternal border and + ankle edema. He was given oxytetracycline intravenously in daily doses of 2 and 3 gm. for 6 months until October, and at that time chlortetracycline and chloramphenicol were added. The temperature gradually returned to normal, but when antibiotics were stopped, the temperature rose. By June the temperature had become normal and remained so. The heart size decreased, but in August an aortic diastolic murmur was first heard. In December, because of persistent cough and sputum, bronchoscopy and bronchography were done, but were unremarkable. During this entire period and until August, 1953, he continued to receive antibiotics, oxytetracycline, 2 gm. daily, and chlortetracycline, 2 gm. daily were given for 6 months ending in May, 1953. In April the patient had been given erythromycin, 4 gm. daily for 2 months. He also received a short 2-week course of bacitracin in July, 80,000 units daily. However, in spite of the continuous use of antibiotics, blood cultures were still occasionally positive for *Staph. aureus*. In August the patient was transferred to the Bronx Veterans Administration Hospital.

On admission he felt well. He had regained much of the weight he had lost but still had some exertional dyspnea. Digitalis had been discontinued in February, and, except for a chronic cough, he had no symptoms. He had had no fever for over 1 year.

The past history was noncontributory. There was no history of heart disease or rheumatic fever.

Physical examination showed a well developed although thin man. The positive findings were confined to the heart, which was not enlarged clinically. The aortic 2d sound was greater than the pulmonic. At the aortic area a harsh systolic murmur was present, as well as a blowing diastolic murmur. The systolic murmur was also heard at the apex.

Examination of the blood revealed a red-cell count of 4,980,000, with a hemoglobin of 15 gm. per 100 cc., and a white-cell count of 11,000, with a normal differential. Urinalysis was normal. The erythrocyte sedimentation rate was 22 mm. per hour. The antistreptolysin titer was 100 to 150 units. X-ray study of the chest disclosed slight enlargement of the heart, but an esophagram did not show enlargement of any specific chamber. An electrocardiogram demonstrated nonspecific ST-segment and T-wave changes. Since admission 10 of 15 blood cultures had grown out *Staph. aureus* that was resistant to penicillin, streptomycin and polymyxin B. It was moderately sensitive to bacitracin, oxytetracycline, chlortetracycline and chloramphenicol, and was sensitive to erythromycin and carbomycin.

Except for a brief febrile episode the patient remained well clinically without antibiotics. Dental examination was made, and x-ray films of bones and sinuses and retrograde pyelograms were taken, but no focus of infection was found. From time to time the quality of the murmurs at the aortic area changed, and they often sounded like a pericardial friction rub. An angiocardiogram did not give any additional information. Some observers thought that a chronic suppurative pericarditis might have been seeding the blood stream. Therefore, on October 22, an exploratory thoracotomy was performed. Except for an enlarged heart, no abnormalities were found. The patient withstood the procedure quite well. He received erythromycin before and after operation, and the organism developed slight resistance to this drug. During this time blood cultures remained positive. In December a new antibiotic, tetracycline, was started in a dosage of 2 gm. daily for 2 months, and since December, 15 blood cultures have been negative. Because of nervousness, the patient was seen by a psychiatrist, who believed that he had schizophrenia. In March, 1954, after receiving tetracycline, he was given 15 electric-shock treatments, with no ill effects.

He has continued to feel well, and blood cultures have remained negative. There have been no changes in the physical findings, and he has gained 15 pounds in weight. It is difficult to be certain whether tetracycline influenced the course of the disease. The process may have healed itself or may be still active in a subclinical form.

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Discussion

The staphylococcus is a rapidly growing organism and one that is easily grown on culture media. A *Staph. aureus* was isolated from both aerobic and anaerobic blood cultures. It grew poorly on simpler mediums when first isolated. On plain agar it tended to form discrete, slightly raised colonies, less than 1 mm. in diameter, and required forty-eight to seventy-two hours for more abundant growth. Gram stain revealed spherical, gram-positive cocci arranged in grapelike clusters typical of staphylococci. After a few subcultures, the organism was trained to grow on ordinary mediums, and fairly profuse growth could be obtained after eighteen hours of incubation. The production of golden pigment was easily detectable in the cultures of the freshly isolated organism, but after a few transplants, the pigment was produced much slower. The organisms subsequently isolated on eighteen occasions were identical in cultural characteristics and morphologic appearance, except that the latest one to be isolated required less time for fairly abundant growth. The organisms from all cultures were facultative anaerobes that were coagulase and mannitol positive, liquefied gelatin and produced nitrites from nitrates. All showed the same sensitivity pattern to antibiotics, as evaluated by the standardized paper-disk method,[4] and were resistant to penicillin and streptomycin, slightly to moderately sensitive to bacitracin, chlortetracycline, oxytetracycline and chloramphenicol and very sensitive to erythromycin and carbomycin. Among organisms isolated on four different occasions, the phage typing of two was 44A and 52A, and that of two others 52A,* and it was believed that these patterns also indicated the similarity of the organisms.

The source of seeding of the blood stream may have been the aortic valve. A chronic abscess in the liver, kidney, spleen, myocardium or prostate is also a possibility, but this would be difficult to prove. Bacterial endocarditis seems the most likely etiology of the chronic staphylococcal septicemia. Staphylococcal endocarditis is not uncommon.[1] No other patient with staphylococcemia has had a variety of antibiotics as this one nor presented such an indolent clinical picture. Friedberg and Bader[5] reported a case treated with bacitracin. Other cases have been treated with chlortetracycline.[6,7]

The important problem in the therapy of staphylococcal infections is the development of resistance to all known antibiotics. In the early days of antibiotics, bacterial resistance was infrequent, but by 1949, *Staph. aureus* had developed penicillin resistance of a significant degree according to Beigelman and Rantz,[3] who also found a correlation between the recovery of resistant staphylococci and the presence or absence of recent penicillin therapy. Sensitive organisms were rarely isolated from infections in persons who had received penicillin, but by 1949 resistant organisms were recovered from lesions in patients who had not received penicillin recently in a significant proportion (34.4 per cent). The authors also reported resistant organisms in 29.4 per cent of healthy carriers who had never received penicillin, and described 2 cases of sepsis due to penicillin-resistant *Staph. aureus* that terminated fatally. Similarly, Needham and Nichols[8] found the prevalence of penicillin-resistant strains of staphylococcus to increase until 1949, when the rise leveled off. They believed that there was a reservoir of penicillin-resistant strains in medical and nonmedical personnel in hospitals since they observed resistant organisms in 20 per cent of 100 healthy nurses; only 10 per cent of 100 outpatients had resistant strains.

Concerning other antibiotics, Needham and Nichols[8] stated that resistance to streptomycin has varied according to the frequency of its use. In 1945 all penicillin-resistant strains were sensitive to chlortetracycline, but by 1951 36 per cent of the strains were also resistant to this antibiotic. Most of these were found in hospitals where oxytetracycline and chlortetracycline were used before and after operation. No resistant organisms to these antibiotics were found in 100 outpatients. Most organisms resistant to chlortetracycline were also resistant to oxytetracycline. No significant number of chloramphenicol-resistant strains were found since this antibiotic is not used too frequently. Infections caused by strains of staphylococci resistant to multiple antibiotics usually were mild, but several fatal infections occurred.

Levinson, Griffith and Pearson[2] reviewed 18 cases of staphylococcal endocarditis, with a mortality of 66 per cent. In addition, of 15 cases studied for resistance, 66 per cent were resistant to penicillin. Chlortetracycline resulted in a cure in 2 cases. These figures emphasize the importance of bacterial resistance to antibiotics.

Fortunately, new antibiotics are being developed continuously, and one of these is erythromycin. An excellent review of its characteristics has been presented by Martin, Nichols and Geraci.[9] This drug is of greatest value in the treatment of gram-positive organisms and in the treatment of infections due to organisms resistant to other antibiotics. However, these authors do not recommend its use in bacterial endocarditis because bactericidal concentrations in the serum are not easily attainable in the dosages commonly used. In addition resistance to erythromycin appears rapidly at times. Also, resistance is likely to develop in its use in chronic infections. The authors have found that erythromycin and carbomycin exhibit crossresistance.

Tetracycline closely resembles chlortetracycline and oxytetracycline both in structure and in antibacterial activity. Finland and his co-workers[10] have shown that there is essentially complete crossresistance among the three antibiotics, and in clinical trials the effects of treatment with tetracycline appeared to be similar to those obtained with oxytetracycline and chlortetracycline. The major clinical difference is considered to be the lower prevalence of gastrointestinal

*The phage typing was performed through the courtesy of Dr. J. E. Blair and Miss M. Carr, of the Bacteriology Department, Hospital for Joint Diseases, New York City, whose help is gratefully acknowledged.

symptoms with tetracycline. It is too soon to state whether or not tetracycline effected a cure in the case reported above. If it did, it would be unusual in view of the data concerning the antibiotic, and this case may represent an exception to those findings.

Summary

A case of *Staphylococcus aureus* septicemia lasting over two and a half years is reported. The infection was resistant to all therapy, but for the present, it is quiescent.

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DOCTORS AFIELD

Alexander Borodin

A. K. Garland

IT is unusual for a man to be able to follow with equal activity two such exacting and diversified fields of endeavor as science and music, without eventually foregoing one for the other. Alexander Borodin was one of the few extraordinary persons successful in both. His chemistry professor, Zinin, used to say: "Mister Borodin, please don't think so much of ballads when here I am believing in your future and trying to train you to succeed me. You can't hunt two hares at the same time."[1] But hunt them he did.

Alexander Porpheyrevich Borodin, born in 1834, was the natural son, it is said, of a Georgian prince. He was brought up by his mother, an unusually wise, sensitive and liberal-minded woman, who hoped that he would study medicine. Accordingly, in 1850, he entered the St. Petersburg Academy of Medicine and Surgery, where he concentrated in chemistry. He passed all his examinations with high grades, and in 1858, after receiving his medical degree, he became house physician at a military hospital. However, the barbarous treatment of the serfs in this institution caused him to turn away from the active practice of medicine to teaching and research.

From 1859 to 1862 he furthered his scientific education in Western Europe, producing eight abstruse papers as a result of these studies. The year 1862 initiated an important period in his career; he was appointed to the position of assistant lecturer in science at the Academy; in 1863 he married, and in 1864 he became professor of organic chemistry at the St. Petersburg Military Academy. He held this chair until his death in 1887. Among his professorial duties were lectureships at the School of Forestry and the School of Medicine for Women (1872), which he helped to found.

From the year of his marriage until 1877 Borodin was particularly active in science and education. Not only did he establish courses in medicine for women; he was an early protagonist of female emancipation in general. He traveled to Germany to observe the laboratories in that country, and while there he carried on a study on nitrogen metabolism in conjunction with Kjeldahl.[2] When he returned to Russia he allowed his students the free use of his own exceptionally well equipped laboratory.

Borodin's published works in science are fairly numerous, including papers on the analogy between phosphorous and arsenious acids from a toxicologic point of view, and on the estimation of salts in mineral waters, and observations on brick tea.[2] Two of his papers have become especially well known: "Researches on Fluoride of Benzole" and "Solidification of Aldehides."[3]

When one considers certain qualities in his character his numerous accomplishments are amazing. He was a genial person — dreamy, sensitive, easy-going and unmethodical; he was happy in his marriage; his hospitality was famous; his house was a menagerie of derelict animals rescued by his wife, and filled with students, friends and relatives, who, one might suspect, exploited him more than a little. He gave freely and lived tremendously. What with his professional duties, his music and his other varied interests he was in a constant tornado of activity — so much so that his health, never robust, at times suffered.

It is as a musician and composer, however, that Borodin is best known. Keenly interested in music as a child, he had received his first musical impressions from military bands where he formed an acquaintance with the musicians and tried to find out how their various instruments were played. At an early age he learned to play the piano, flute and cello.

When he was nine years old Borodin composed a polka, and at thirteen he wrote a concerto for the flute. Even in those days he was an extraordinarily well rounded person, having an extensive knowledge of and gift for languages and the natural sciences. Some of his other interests included modeling in clay and painting, for which he ground his own pigments. He had ample time to develop these interests because he was brought up largely by women and had few friends of his own age.

While at the Academy he redoubled his activities in music, studying and mastering polyphony. He organized a string orchestra with thirty of his friends

and composed some chamber music and songs, none of which were published. Though equally devoted to science and music, as a matter of duty he chose the former for a career, remaining only a music lover until the age of twenty-eight, when he made his first earnest effort in that field.

Because of his deficiency in technical knowledge Borodin began study with Balakirev in 1862. During his internship at the military hospital he met Moussorgsky; in 1865 his life-long friendship with Rimsky-Korsakov began, and he came in contact with Cui while sojourning in Western Europe. Thus assembled that unique group of five "amateurs," Borodin included, who strove so ardently together to bring Russian music into its own.

The hopes of the "Mighty Five" were to found a school of nationalistic composition coming from the already rich stores of folk song; to cleanse Russian music drama of Italian and German influences; and to force an indifferent and even hostile audience (both at home and abroad) to recognize its merit.

The trend toward purely Russian music had been put in motion by an earlier dilettante composer, Michael Glinka, his music taking its origin directly from folk song and Orthodox Church liturgy. Another pioneer who laid the groundwork of the "Five" was Alexander Dargomijsky, who, with Glinka's object in mind, was able to progress a little farther. Dargomijsky influenced Balakirev, who in turn extended his sphere of influence to the other members of the group.

This quintet, who in general followed and added to the spirit of Glinka and Dargomijsky, did not bind themselves by any particular rules or adhere blindly to academic theories. Each was free to use his own methods, provided they were in the common direction, and advice and collaboration were interchanged with remarkable freedom. It is also remarkable that each composer retained his own individual characteristics. It might be said that this philosophy helped greatly to save the group from disintegration, the fate of many similar movements.

Among the members Balakirev was the best equipped with technical background; as teacher and energetic adviser he was the patriarch of the organization. Cesar Cui, whose work as a composer was negligible, was the propagandist of the Band. "He waged furious and unceasing war on the very cosmopolitanism that he practiced in his own work . . . and sought to dispel aristocratic prejudice and academic ridicule."[4] Rimsky-Korsakov was the master of orchestration, and Moussorgsky was the realist, the daring experimenter in new harmonies and the "supreme genius" of Russian opera. Borodin was the "all-round" man of the group. He was considered by some to have been, in his music, the most typically Russian, and he has had, perhaps, the strongest influence on contemporary Russian music.[4]

Borodin's contact with Balakirev stimulated his technical interest in music. Moussorgsky was the first to infect him with the nationalistic spirit, though he retained a deep respect for the music of Beethoven. Rimsky-Korsakov acquainted him with the possibilities of Orientalism and native folklore in music drama, and Cui traveled with him on his most successful music tours of Europe, introducing him to many who were sympathetic to their movement. Borodin also owed much to the influence and encouragement of Liszt, that "untiring champion of all artistic progressivism of whatever school, who wrote more bad music and helped more good than any other man in the nineteenth century."[1]

Borodin's first symphony (E flat) was his earliest serious composition; it marked his debut as a composer and was perhaps the first of such works to attain recognition outside Russia. Begun in 1862, it took five years to complete. (He had a habit of immersing himself in dozens of projects simultaneously.)

His second symphony (in B), though begun in 1860, was not published until 1876. It was considered to be a monument in the progress of Russian symphonic development. (Incidentally, this music was based on themes already outlined for his famous opera "Prince Igor," which was not finished until after his death when Rimsky-Korsakov and Glazounov rescued the score.) A third symphony was also in the making at the time of his death and was posthumously finished and published by Glazounov. Borodin also composed a tone poem, two string quartets and more than twenty very lyrical songs.

He died at the height of his musical success at a masked ball in his house; as the obituary in the *Lancet* succinctly states, "from cardiac paralysis, probably from embolism of highly diseased coronary arteries."[2]

From the vantage point of time one can see more clearly his position in art. It is said that Borodin was as much the master of symphony at that time as Brahms, and that his music has all the wholesomeness of Beethoven.[4] He had the three basic elements of music — melody, harmony and rhythm — completely under control. He was an amateur in music only because he did not make that field his profession; there is nothing amateurish in his mature compositions. His music, superlative in itself, is important because it is among the first Russian "national" works to acquire international recognition.

In the words of Sir Henry Hadow: "No musician has ever claimed immortality on so slender an offering. Yet if there be, indeed, immortalities in music, his claim is incontestable."[1]

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41051

PRESENTATION OF CASE

A forty-four-year-old housewife was admitted to the hospital because of continuous pain in the upper left side of the chest.

The patient first learned that she had heart disease ten to fifteen years previously, when exertional dyspnea developed. Seven years before admission signs of congestive heart failure occurred during the sixth month of her eleventh pregnancy. Examination at that time showed a chronically ill, cyanotic woman with marked engorgement of the neck veins. The cardiac impulse was in the anterior axillary line in the fifth intercostal space. The mitral first sound was accentuated; the pulmonic second sound was split and greater than the aortic. Grade 2 systolic and diastolic murmurs were present in the aortic area, and Grade 2 diastolic rumbles and a Grade 4 systolic murmur at the apex as well as under the xiphoid process. There was atrial fibrillation. The liver edge, which was palpated 8 cm. below the right costal margin, was tender and slightly pulsatile. Accordingly, she was placed on a cardiac regimen, and sterilization was advised but was refused. The patient was almost completely bed ridden because of dyspnea and attended the medical clinic during the next year and a half. She was treated with digitalis, low-sodium diet and limitation of activity. An electrocardiogram then showed partial atrioventricular block, with widening of the PR interval and dropped beats. The sedimentation rate was 22 mm. and a year later 26 mm. per hour. During the following years she had dyspnea but did most of the housework for her 10 children. She had not returned to the clinic for several years. Three months before admission she entered another hospital in the ninth month of her twelfth pregnancy because of increasing epigastric distress and nausea. She was given digitalis and diuretics, and a normal delivery subsequently occurred. At that time a bromsulfalein test showed 20 per cent retention of the dye. Thymol turbidity was 3 units, and the albumin 2.1 gm. and the globulin 4.3 gm. per 100 cc. Twenty-seven days after delivery she returned home. This was followed by a week at a convalescent home, where an epidemic of hepatitis was said to be in progress. Thereafter, during the month before admission, she was bed ridden, with orthopnea relieved by 4 or 5 pillows, a swollen abdomen and legs and occasional bouts of fever. Eight hours before admission, while dozing in a chair, she was suddenly afflicted with continuous pain in the second and third left intercostal spaces, greatly aggravated by deep breathing. She denied recent hemoptysis, chills, fever, cough, cyanosis or palpitations but later admitted having had occasional abdominal pain and small hematemeses while at home.

Physical examination revealed a very frail and ill woman with moderately severe dyspnea. There was questionable scleral icterus. Over the right lower lobe posteriorly there was dullness to percussion and decreased fremitus and voice sounds. Above this, and also over the left-lung base posteriorly, there were fine crepitations. Anteriorly, pleuropericardial and pleural friction rubs were heard over the site of the chest pain. The neck veins were engorged and pulsating. There was pitting edema of the legs up to the groins and over the sacrum. The right calf measured 31 cm. in circumference and the left 29 cm. Cyanosis was slight. The heart was enlarged, its borders extending 6 cm. to the right of the midline and to the anterior axillary line in the sixth intercostal space on the left side. A diastolic thrill and a Grade 2 low rumbling murmur were present at the apex. Along the left sternal border there were a systolic thrill and harsh Grade 2 systolic and soft Grade 1 diastolic murmurs. The systolic thrill and murmur were transmitted to the axilla and base. A systolic murmur was also heard in the tricuspid area. The pulmonic second sound was considerably louder than the aortic. The first mitral sound was snapping and louder than the second. The liver edge extended to below the level of the right iliac crest, below the umbilicus and 3 or 4 cm. below the left rib margin. The spleen was palpable 3 cm. below the left costal margin.

The temperature was 101.2°F., the pulse 104 at the apex and 96 at the wrist, and the respirations 26. The blood pressure was 125 systolic, 80 diastolic.

Urinalyses showed a + or ++ test for albumin on four occasions and ++ to +++ tests for bile; the sediment contained a few white cells and 10 to 30 hyaline casts per high-power field. Urobilin was positive in a dilution of 1:16 and questionable in a dilution of 1:32. Two determinations of the sedimentation rate were 3 mm. per minute. The hematocrit was 47 per cent. With transfusions the

hemoglobin increased from 9.5 to 16.5 gm. and was finally 14 gm. per 100 cc. The white-cell count rose from 16,600 to 34,000 terminally, and the neutrophils also increased relatively from 82 to 95 per cent. The serum bilirubin was 4.4 mg. per 100 cc., and the sodium 127 milliequiv., the chloride 94 milliequiv., and the carbon dioxide 26.5 milliequiv. per liter. The nonprotein nitrogen rose from 52 to 70 mg. per 100 cc. during the first four days in the hospital. An electrocardiogram on the first two days showed atrial flutter and bigemini consistent with, but not diagnostic of, myocardial or pulmonary infarct. A second electrocardiogram demonstrated atrial flutter, with 4:1 block but no evidence of a pulmonary infarct. A roentgenogram of the chest revealed a slight increase in pulmonary congestion, free fluid in the right pleural cavity and probably a little fluid in the left, but no good evidence of pulmonary infarct (Fig. 1). The blood Hinton test was negative. Blood cultures on six occasions were reported as negative apart from a growth of *Staphylococcus albus* in one.

FIGURE 1. *Posteroanterior View of the Chest, Showing Marked Cardiac Enlargement, Pulmonary Vascular Congestion and Pleural Effusion on the Right.*

On the second hospital day a total of 100 mg. of Dicumarol was given in two 50-mg. doses at 2 a.m. and 8 p.m. On the same day a specimen received about midday was reported as showing a prothrombin time of 19 seconds (normal, 13 seconds). The next day the prothrombin time was 16 seconds (normal, 13 seconds), and 75 mg. of Dicumarol was given. The white-cell count was 7500. On the fourth day the prothrombin time was again 16 seconds (normal, 13 seconds), or 25 per cent, and a further 75 mg. of Dicumarol was given. Six hundred and sixty cubic centimeters of clear, serous fluid was aspirated from the chest. On the fifth day the prothrombin time was 29 seconds (normal, 13 seconds). The white-cell count had risen to 28,000; 200 mg. of vitamin K_1 was given orally. The patient was restless all day and had diffuse abdominal tenderness, pain in the left side of the abdomen, nausea and vomiting of material that gave a ++++ guaiac test. Watery stools also gave +++ guaiac tests. The left arm became edematous, and a tender cord was felt in the left axilla. The blood was 80 systolic, 50 diastolic, the pulse 90, and the respirations 12. The chest was clear except for a few basal rales. The abdomen was greatly distended, diffusely tender and tympanitic, and peristalsis was absent.

On the sixth day the patient was semicomatose; the gastric aspirate was watery and dark brown. Catheterization obtained only 80 cc. of dark-amber urine, in which there were no red cells. The temperature was 99.6°F., the pulse 120, and the respirations 30. The blood pressure had fallen to 60 systolic, 40 diastolic. Bowel sounds were still not present in the diffusely tender and tympanitic abdomen. The urine had a specific gravity of 1.014 and gave a + test for albumin; the sediment contained many hyaline casts but no red cells. Again, Dicumarol was withheld, and instead vitamin K, 5 mg., was given intramuscularly. The prothrombin time was 30 seconds (normal, 13 seconds).

Drugs also given during treatment were digitalis, digitoxin, quinidine, ammonium chloride, mercurial diuretics, potassium chloride, chloral hydrate, phenobarbital, atropine, Demerol and morphine. Neither salicylates nor any other anticoagulant was ever given.

On the seventh hospital day the hypotension, tachycardia, stupor and abdominal distention increased. Although the temperature was essentially normal throughout the hospital course and reached only 99.5°F. terminally, the pulse started rising about forty-eight hours before death, finally reaching 130; similarly, respirations increased to 35 per minute. The output of the urine had fallen to below 400 cc. a day during the last four days. Vitamin K, 5 mg., was again given intramuscularly, and the prothrombin level had returned shortly before death to 25 per cent of normal.

DIFFERENTIAL DIAGNOSIS

DR. DAVID D. RUTSTEIN*: May I see the x-ray films?

DR. C. C. WANG: The examination of the chest shows considerable pulmonary congestion on both sides and a patchy increased density in the right-lower-lung field overlying the right cardiophrenic angle that could be an area of localized edema and pneumonitis; certainly, one cannot rule out pulmonary infarction (Fig. 1). The heart is greatly enlarged, apparently in all directions, and has no char-

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acteristic configuration. There is free fluid in both pleural cavities, somewhat more on the right side. The main pulmonary artery is slightly enlarged.

DR. RUTSTEIN: This patient had had a long chronic course of heart disease, the existence of which was first called to her attention during her eleventh pregnancy. This is not unusual since at the Boston Lying-in Hospital almost half the patients with a definite diagnosis of organic heart disease have that diagnosis made for the first time during a pregnancy. In this patient with long-standing heart disease and a slowly progressive, chronic course, each of two attacks of heart failure was precipitated by a pregnancy. It is remarkable how long persons with severe heart disease of this sort can live and carry on a relatively useful life and yet have acute congestive heart failure precipitated by the burden of pregnancy.

The burden of pregnancy on the circulation manifests itself by increased oxygen consumption, plasma volume and red-cell mass, tachycardia and an increased cardiac output associated with an increased uterine blood flow to supply the fetus whose oxygen requirement per gram of tissue is greater than that of the patient. Burwell et al.[1] have made the important observation that this burden is continuous and carried for twenty-four hours each day and not discontinuous like that brought about by physical exertion.

There are four classic signs indicative of a poor prognosis of heart disease in pregnancy, and all were present in this patient. The first is the age of the patient. The death rate at the Boston Lying-in Hospital among patients with organic heart disease rises sharply at the age of thirty and continues to rise rapidly after the age of thirty-five.[2] This patient was thirty-seven when she had her first attack of acute congestive heart failure. Changes related to aging, not as yet defined, must occur in the myocardium. Sports that require sudden expenditures of effort can only be participated in successfully by young athletes. Congestive heart failure from hyperthyroidism in persons with otherwise normal hearts occurs primarily among those over forty years of age. Unpublished studies done in our laboratory of the circulation time by the cyanide method on normal subjects recently recovered from pneumococcal lobar pneumonia shows that the rate of circulation slows with age. The other three classic signs of serious prognosis, all of which were present in this patient, are marked cardiac enlargement, atrial fibrillation and a history of previous congestive heart failure. Whenever any one of these four signs of serious prognosis is present early in pregnancy in a patient with organic heart disease, interruption of the pregnancy to save the life of the mother must seriously be considered.

It is clear that the patient had continuing low-grade congestive heart failure beginning with a first acute attack during her eleventh pregnancy. Exacerbation occurred during the twelfth pregnancy, continuing up to the present hospital admission. This last episode began two months after the end of the twelfth pregnancy with sudden pain, greatly aggravated by deep breathing, in the left side of the chest — that is, pleural pain. The most probable cause of such a pain in this patient with slowed circulation is pulmonary infarction. Another much less likely possibility is rheumatic pneumonia, which usually does not cause pleural pain. She may have had an acute cardiac episode, but I cannot make a diagnosis of acute myocardial infarction. The absence of x-ray findings does not rule out pulmonary infarction since large areas of the lung fields were obscured by the enlarged heart and because one of a series of small pulmonary infarctions could have involved the pleural surface and produced pain. The tender cord in the left axilla was another manifestation of blood-vessel thrombosis. The staff apparently had the same impression since anticoagulant therapy was given. This clinical history provides a good illustration of the occasional difficulty of balancing the effects of anticoagulant therapy and vitamin K.

Superimposed disease, particularly subacute bacterial endocarditis, must be considered. Pregnant patients have a transient bacteremia during delivery, which may initiate subacute bacterial endocarditis in patients with certain pre-existing rheumatic or congenital cardiac lesions, such as mitral or aortic disease, patent ductus arteriosus and septal defect. In support of this possibility, the spleen was palpable and some of the thrombotic manifestations might have been embolic, but the blood cultures were negative. I cannot either diagnose or rule out subacute endocarditis; the house staff could not have thought she had this disease, for she received no treatment for it.

The diagnosis of the heart disease is based on the following findings: the heart was markedly enlarged, its border extending 6 cm. to the right and to the anterior axillary line on the left in the sixth intercostal space. The sounds at the apex were those of mitral insufficiency and stenosis in a patient with atrial fibrillation. A systolic thrill was transmitted to the axilla and to the base of the heart, but nothing was said about its transmission along the vessels of the neck. Although an aortic second sound was heard, I assume that the systolic thrill and systolic and diastolic murmurs at the base indicated insufficiency and some stenosis of the aortic valve.

A superimposed congenital lesion is always possible in such cases, but if this patient had a septal defect or patent ductus arteriosus, I cannot diagnose it.

The usually confusing difficulties of diagnosing heart disease in a pregnant patient really did not exist here because of the far-advanced heart disease. It is well to point out, however, that diagnosing moderate grades of heart disease in pregnancy is not a simple matter and is dependent on identifying a dias-

tolic murmur, characteristic cardiac enlargement or signs of congestive heart failure, particularly pulmonary rales or a diminished vital capacity. Pregnant patients without heart disease have dyspnea and tend to have swollen ankles, tachycardia and blowing systolic murmurs, all of which disappear after delivery. When one suspects but cannot diagnose heart disease during pregnancy, the patient should be re-examined after delivery.

I believe that this patient had far-advanced rheumatic heart disease with mitral stenosis and insufficiency, aortic insufficiency with some stenosis, and probable tricuspid insufficiency. The question of tricuspid stenosis is also posed because of the diastolic murmur heard over the xiphoid process on the previous admission.

The preventive aspects of this case should be considered. Nothing could have been done about the rheumatic fever since there was no recognized attack of acute rheumatic fever at any time. Moreover, the agents now known to be effective in the prevention of rheumatic fever by adequate treatment of infection with the beta-hemolytic streptococcus were not available during her childhood. Since more than half the patients whose heart disease is discovered for the first time during pregnancy have no previous history of rheumatic fever, this situation is not an unusual one.

This patient's last illness was precipitated by her twelfth pregnancy. It is difficult to state whether after the eleventh pregnancy at the age of thirty-seven the likelihood of a twelfth pregnancy would justify the operative risk of sterilization, but birth control as a preventive measure to protect the life of the mother was indicated. There may, however, have been religious reasons for not administering these preventive measures.

Bleeding from the gastrointestinal tract in the presence of a distended, tender abdomen and portal congestion was probably due to a mesenteric thrombosis although a certain amount of the bleeding may be attributed to the anticoagulant. It seems clear from the record that the staff thought that the gastrointestinal bleeding resulted from too much Dicumarol. It is interesting to note the large number of thrombotic manifestations that developed in this patient after the beginning of anticoagulant therapy.

DR. DANIEL S. ELLIS: Why do you think the patient had an albumin of 2 gm. and a globulin of 4 gm. per 100 cc.?

DR. RUTSTEIN: I cannot tie many of the chemical findings in this patient to the clinical disease. She was constantly losing albumin in the urine. The duration of this albumin loss is unknown, and the adequacy of her diet during her many pregnancies is not stated.

DR. ELLIS: Do you think she had cirrhosis?

DR. RUTSTEIN: I think she had some cirrhosis, but I do not know how much. I also wonder about the accuracy of the albumin measurement; it was done only once. Many of the chemical findings, although not characteristic, are not inconsistent with a prolonged course of congestive heart failure.

DR. ALLAN L. FRIEDLICH, JR.: The physicians on the Service believed that the patient had had a pulmonary infarct in spite of its absence in the x-ray films. The heart was so large that a great deal of lung could not be seen in the films. One of the major discussions was whether the tendency to embolism should be treated by ligation of the femoral veins, by ligation of the inferior vena cava or by anticoagulants. The last, of course, was chosen, and anticoagulants were given with great caution. Terminally, we could not be certain whether there was a mesenteric thrombosis, embolism or simply massive bleeding into the gastrointestinal tract as the result of coagulation defect.

DR. WALTER BAUER: She had no peristalsis.

DR. FRIEDLICH: That is correct, and we considered it in favor of a mesenteric embolus. We certainly thought that she had severe impairment of liver function due to long-standing hepatic congestion. An interesting point was that she continued to bleed when the prothrombin levels were in the ordinary therapeutic range and died when the prothrombin time was not extremely prolonged.

DR. BENJAMIN CASTLEMAN: Dr. Bauer, have you any comment?

DR. BAUER: I am glad that Dr. Rutstein commented on heart disease in pregnancy in such detail because our experience here is limited. I agree that this patient had severe rheumatic heart disease, with severe congestive heart failure and pulmonary infarction. I think both the hepatic and renal abnormalities were manifestations of long-standing heart failure. We all know that the use of anticoagulants is not without danger. In this case they were administered in small doses. In spite of the cautious procedure, it was necessary to discontinue Dicumarol and give vitamin K. It is difficult to determine whether the gastrointestinal bleeding was the result of the anticoagulant therapy or of mesenteric thrombosis. Because of the absence of peristalsis, I favor a diagnosis of mesenteric thrombosis or embolism.

One blood culture was positive for *Staph. albus;* that lone finding is always difficult to evaluate. It is important to remember that subacute endocarditis due to the staphylococcus can for a time be a benign affair and is easy to miss.

DR. RUTSTEIN: The *Staph. albus* is a fairly easy micro-organism to grow. I disregarded it because it was found in only one culture. It should have been found more frequently if it had been associated with the illness.

CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and insufficiency.
?Mesenteric thrombosis or embolism.
Pulmonary embolus.

Left-axillary-vein thrombosis.
Cardiac cirrhosis.

Dr. David D. Rutstein's Diagnoses

Rheumatic heart disease, with mitral and aortic stenosis and insufficiency, and tricuspid insufficiency and ?stenosis.
Mesenteric thrombosis or embolism.
Pulmonary infarction.

Anatomical Diagnoses

Rheumatic endocarditis, acute and chronic, with mitral stenosis and insufficiency and aortic and tricuspid stenosis.
Massive hemorrhage (?Dicumarol effect) into small and large intestines, stomach, ovary, lungs and right adrenal gland.
Central congestion and necrosis of liver, severe, with extensive hemorrhages.
Anasarca.
Pulmonary infarcts, lower lobes.
Icterus.

Pathological Discussion

Dr. Castleman: At autopsy we found, as we had expected, an enlarged heart with involvement of the mitral, aortic and also the tricuspid valves. The tricuspid valve was mildly but definitely stenotic. The mitral valve had a very small lumen with a row of beads around it — a characteristic active rheumatic endocarditis. The aortic valve showed the same beading below the free edge along each cusp. The liver was very markedly hemorrhagic — about as severe hemorrhage as I have ever seen with congestive heart failure. There was central necrosis, with bleeding into it. In the markedly hemorrhagic areas the hemorrhage had covered up the necrosis. The stomach, which was full of blood, contained an ulcer. The intestines were also full of fresh blood, but we were unable to find any true ulcers in the intestines; this was therefore an extensive hemorrhage without any evidence of infarction of the bowel and no evidence of thrombosis of any of the vessels of the gastrointestinal tract. There were infarcts in both lower lobes of the lungs. I gather that the cause of the jaundice was a combination of passive congestion in the liver and pulmonary infarcts in the presence of the congestive heart failure and the inability of the liver to handle the large amount of hemosiderin coming from the infarcts. I think we have to attribute the hemorrhages to a large extent to the anticoagulants.

Dr. Rutstein: Was there any evidence of rheumatic activity in the myocardium?

Dr. Castleman: We found some suggestive Aschoff bodies, but not many; I believe the valve lesions were pathognomonic of activity.

Dr. Rutstein: I think there is another important lesson in this case. Rheumatic activity serious enough to cause cardiac involvement may not be recognizable clinically as acute rheumatic fever. This "iceberg concept" of rheumatic fever — that is, one in which most of the activity lies below the level of clinical recognition — is now supported by pathological evidence of activity in the myocardium at operation for mitral commissurotomy in patients without any clinical evidence of acute disease. This is important in evaluating the treatment of this illness because agents that obliterate evidence of activity do not necessarily cure the patient. For example, the rebound phenomena in which rheumatic symptoms occur when treatment with ACTH or cortisone is stopped must mean that the patient still has active disease that was suppressed but not obliterated by the therapeutic agents.

A Physician: Were there any thromboses in the mesenteric veins?

Dr. Castleman: No; there were no thromboses in the mesenteric veins.

There was evidence of heart failure, with a great deal of fluid in various cavities. Both ovarian veins were thrombosed, and there was a great deal of hemorrhage in the pelvis. The ascitic fluid was hemorrhagic.

Dr. James H. Currens: Were there thromboses in the arm veins?

Dr. Castleman: Yes.

A Physician: I think it is worthy of note that the level of the prothrombin in this patient did not exceed that of many patients who have successfully passed through infarction on Dicumarol therapy.

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CASE 41052

Presentation of Case

A forty-eight-year-old machinist entered the hospital because of severe back pain.

Two weeks previously he noted the onset of mild pain in the lower back, with radiation around to the front, which was increased by coughing. This lasted for two days, disappeared spontaneously, recurred nine days later and lasted for one day. At this time he had a temperature of 101°F. During the day before admission the pain recurred in the right flank, was relieved by doubling over and was increased by coughing, deep breathing or lying on the right side. He had no urinary-tract symptoms and denied chest pain, hemoptysis, weight loss and anorexia. He had had a slight cough for two weeks, however.

A stone had been removed from the left kidney six years previously. A few months before admission he was told that he had an ulcer and was put on a milk diet; since then he had been drinking more than 2 quarts of milk daily.

On physical examination he appeared to be fairly comfortable. The only significant findings were slight tenderness deep in the right upper quadrant of the abdomen and a nontender liver palpable 2 fingerbreadths below the costal margin. There was also moderate right-costovertebral-angle tenderness.

The temperature was 99.2°F., and the pulse 82. The blood pressure was 118 systolic, 80 diastolic.

Examination of the urine was negative except for 2 to 5 white cells and 1 or 2 red cells per high-power field in the sediment. Examination of the blood showed a hemoglobin of 13.5 gm. per 100 cc. and a white-cell count of 11,450. The alkaline phosphatase was 9.5 units, the nonprotein nitrogen 24 mg., the total protein 6.5 gm., the calcium 9.6 mg., and the phosphorus 3.9 mg. per 100 cc. The prothrombin time was 100 per cent. An x-ray film of the chest showed small calcific densities in the right apex, a few strands of increased density in both lower-lung fields and anterior wedging of several lower dorsal vertebras. A plain film of the abdomen was normal. An intravenous pyelogram demonstrated a small stone in the right kidney just below the lower calyx and changes suggesting old pyelonephritis in the left lower calyx.

By the day after admission, on supportive therapy, the pain had disappeared, and the patient was discharged on Gantrisin and a low-calcium diet.

FIGURE 1. *Posteroanterior View of the Barium-Filled Stomach, Showing Irregularity of the Lesser-Curvature Aspect of the Gastric Antrum and Narrowing of the Postbulbar Portion of the Duodenum.*
The liver is greatly enlarged.

Second admission (nine days later). Six days later, when he was seen in the Stone Clinic, the urine gave a ++ Sulkowitch test and showed 1 to 3 white cells per high-power field in the sediment. Three days after the clinic visit he was readmitted to the hospital because of persistent, aching pain in the right upper quadrant, lower right side of the chest and back. Pain had been intermittently present in the right side of the chest since an attack of pneumonia eight years previously and was worse during cold weather. He stated that this was different from the "stone pain." Since leaving the hospital he had had episodes of fever without chills and severe night sweats for the preceding two weeks, but no recurrence of the stone or ulcer pain or urinary symptoms. He had, however, noted abdominal swelling during the preceding week and admitted having had black stools during the previous month.

Physical examination showed a man who appeared to be chronically ill, in no acute distress but in pain. Significant findings were dullness at the right-lung base, with decreased breath sounds and tactile and vocal fremitus. The epigastrium was large, protuberant, hard and fixed. The liver extended well across the midline; its edge was felt 8 fingerbreadths below the right costal margin and was hard, tender and smooth.

The temperature was 99°F., the pulse 90, and the respirations 20. The blood pressure was 150 systolic, 90 diastolic.

A routine urinalysis was negative. Examination of the blood revealed a hemoglobin of 11.5 gm. per 100 cc. and a white-cell count of 18,000, a bromsulfalein retention of 33 per cent and a prothrombin time of 100 per cent. The total protein was 6.2 gm., with an albumin-globulin ratio of 3.8:2.4, and the bilirubin 1.4 mg. per 100 cc. The cephalin flocculation was negative in twenty-four and forty-eight hours. A stool guaiac reaction was ++++. A barium-enema examination showed difficulty in filling of the ascending colon and cecum.

Penicillin, streptomycin and Gantrisin were started, and other supportive therapy given. Sigmoidoscopy to 25 cm. on the day after admission was negative. A gastrointestinal series three days after admission (Fig. 1) demonstrated slight separation of the stomach from the diaphragm and displacement of the stomach and duodenum by an enlarged liver; the peristaltic pattern of the antrum was "somewhat more irregular than usual." An x-ray film of the chest showed bilateral fluid and elevation with impaired movement of the right leaf of the diaphragm. On the next day the serum alkaline phosphatase was 17.0 units, and the bilirubin 0.9 mg. per 100 cc.; bromsulfalein retention was 26 per cent, and cephalin flocculation and total protein were as before. The white-cell count was 11,550, with 85 per cent neutrophils. The temperature had stayed below 100°F. On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Grant V. Rodkey*: May we see the x-ray films? I need all the help that I can get.

Dr. John F. Gibbons: In the first films that were taken of the chest there are old calcified scars in the right lung and platelike areas of atelectasis in both lower lobes, with no evidence of fluid in the pleural cavities. The heart is not enlarged. The films of the abdomen demonstrate a small calcification, which later is shown to be in the lower pole of the right kidney, marked enlargement of the liver, particularly of the left lobe, and displacement downward of the colon. The pyelogram taken on the next day shows clubbing of the upper-pole calyxes of the right kidney, a small stone in the lower pole and a deformity of the minor calyxes in the lower pole of the left kidney, all of which are probably due to bilateral pyelonephritis. The kidneys are not displaced, and their outlines appear normal; the ureters appear normal.

Dr. Rodkey: Is there evidence of hilar-lymph-node enlargement on the chest film?

Dr. Gibbons: I do not see any. Subsequently, after another two weeks, the chest films give more evidence of atelectasis in the right lower lobe, with some elevation of the diaphragm and a little fluid in the costophrenic sulcus. On the next day, during a barium-enema examination, the fluoroscopist said that the ascending colon filled with difficulty. There is incomplete filling of the colon; however, I do not see any intrinsic disease in it. There may have been enough fecal material in the colon and perhaps some pressure on it by the liver to prevent its filling. After evacuation the edges of the large bowel appeared to be normal. I do not think there is a lesion in the colon.

Dr. Rodkey: Was a gastrointestinal series done?

Dr. Gibbons: Yes; the next day. The fluoroscopist described irregular peristalsis in the antrum and pressure on the stomach and duodenum by the enlarged liver. The stomach is displaced to the left, and there is an indentation on the first portion of the duodenum extrinsically. There is something else that worries me: on the films there seems to be a persistent abnormality and narrowing of the postbulbar portion of the duodenum, and again the prepyloric portion of the antrum does not fill out normally. I do not know whether it was ever seen to fill out under the fluoroscope. Actually, only on the large films is this portion seen; the spot films show the gastric antrum and the first portion of the duodenum but not the descending limb of the duodenum. Here is a film on which the lumen appears to open out quite well, but there seems to be some irregularity of the mucosa in the same region.

Dr. Rodkey: What would you say about the statement that the stomach seemed separated from the left leaf of the diaphragm?

Dr. Gibbons: I think the separation is probably not significant. The gastric fundus is fairly close to the diaphragm.

*Assistant in surgery, Massachusetts General Hospital.

Dr. Rodkey: You think that that may be reasonably explained by traction on the stomach by the liver. Is there evidence of esophageal varices?

Dr. Gibbons: Apparently not. The last films of the chest demonstrate more noticeable elevation of the right leaf of the diaphragm and atelectasis above it. A grid film of the chest does not contribute anything further. I do not see any abnormal gas shadows below the diaphragm.

Dr. Rodkey: Would you comment on the bones? There is a statement in the protocol that there was wedging of the thoracic vertebras.

Dr. Gibbons: There are some elongation and narrowing of the vertebras, with irregularity anteriorly, suggesting healed juvenile epiphysitis. We see that not uncommonly; I should think it has no clinical significance in an adult.

Dr. Rodkey: This case has a great many abnormal findings, with minimal indications of their source. As I thought about the problem, I wondered about the possibilities of bone disease, which was brought to mind by the past history of renal stones, by symptoms that suggested an ulcer to some physician and by the question of some demineralization of the spine. There is apparently no reason to think that this man had intrinsic metabolic bone disease such as hyperparathyroidism. Whether he had considerable metastatic carcinoma to bone is another question. The elevation of the alkaline phosphatase is interesting. We know either that this indicates osteoblastic activity or that it may be the result of obstructive or metastatic disease of the liver. Probably, it is more reasonable to assume that the elevation of the alkaline phosphatase was caused by interference with the function of the liver. There was slight elevation of the bilirubin, a normal prothrombin time and a definitely increased retention of the bromsulfalein; the significance of the value of the bromsulfalein level is in question because the bilirubin level was elevated at the times it was done. There certainly was, however, some chemical evidence of impairment of liver function. Added to this is the liver enlargement — which, apparently, if I am to believe the observers on two occasions, had taken place rapidly. I think from surveying the x-ray films that the liver was large at the time of the first admission so that there is some question whether there was a significant change. The total protein was a low normal value, but there was no abnormality of the albumin-globulin ratio; on one occasion the albumin seemed to be lower than normal, but the globulin fell within the normal range.

The question of sarcoidosis should be raised. The patient had pulmonary fibrosis to a certain degree, enlargement of the liver and elevation of the alkaline phosphatase — all of which may be associated with sarcoidosis. Tarry stools have been reported in cases of sarcoidosis as the result of bleeding from granulomatous lesions in the small bowel.

It seems to me that by far the most likely diagnosis

is a carcinoma arising somewhere in relation to the gastrointestinal tract and metastasizing to the liver and probably to the lungs or, at least, to the thoracic lymphatics. Dr. Gibbons's films point to the region of the first or second portion of the duodenum. Even if the irregularity in the outline of the bowel had not been observed, my own first thought would be carcinoma of the pancreas, with which pain in the back is fairly common. Although this did not follow the typical pattern of carcinoma of the pancreas, that diagnosis should be brought immediately to mind. Carcinoma of the stomach might present the same picture, but there is not enough evidence of an x-ray deformity of the stomach for me to make that diagnosis.

In summary and rather hastily I am going to say that I think this man had carcinoma of the pancreas, metastatic to the liver and thoracic lymphatics. I doubt if he had metastases to the bone, and I do not believe that the renal stones or chronic pyelonephritis was related to the present illness.

A PHYSICIAN: Does Dr. Rodkey include carcinoma of the ampulla of Vater with carcinoma of the pancreas?

DR. RODKEY: I should not, having seen the x-ray films, suggest a carcinoma of the ampulla of Vater because I think that the visualized defect of the duodenum is proximal to the ampulla. On the other hand, slight jaundice may occur from pressure on the common duct by carcinoma of the pancreas or by lymph nodes along the gastrohepatic ligament. Although carcinoma of the ampulla is possible, I should place that diagnosis second or third on the list.

DR. EARLE M. CHAPMAN: The possibility of Charcot's fever with biliary-tract disease and engorgement of the liver occurred to me. I was surprised to see that no Graham–Cole test was done.

DR. RODKEY: I had not considered that possibility.

DR. JACOB LERMAN: I should like to ask Dr. Rodkey how he explains the bleeding from the bowel?

DR. RODKEY: I think that there was an erosion into the duodenum from a carcinoma primary in the pancreas.

CLINICAL DIAGNOSIS

Primary tumor of liver.
?Liver abscess.

DR. GRANT V. RODKEY'S DIAGNOSIS

Carcinoma of pancreas, with metastases to liver and extension to duodenum.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of stomach, with extension to liver and omentum and with metastases to liver, abdominal lymph nodes and adrenal glands.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: At operation the surgeon entered an abdomen full of carcinoma involving the liver and omentum. In his note the surgeon stated that he could not tell where the primary tumor was because everything in the region of the head of the pancreas and distal stomach, which was covered with involved omentum, was bound together. All he did was take a biopsy, which we reported as showing metastatic adenocarcinoma. The patient went home after a few weeks but returned within a month and died in the hospital. At autopsy we found multiple nodules of metastatic carcinoma in the liver, which weighed over 5 kg. The retroperitoneal lymph nodes along the abdominal aorta were completely involved with tumor. Since we found no involvement of the vertebras and none of the pancreas, I think the pain in the back may well have been produced by metastases in the lymph nodes in the retroperitoneal region. The primary tumor was in the antrum of the stomach but did not extend to the pylorus. It was on the anterior wall, with an ulcer about 5 cm. in diameter, which extended to the serosa of the stomach and to the undersurface of the liver so that it was adherent to the liver at that point. There were metastases to other parts of the body including the adrenal glands.

DR. GIBBONS: Was the duodenum bound down by the metastases?

DR. CASTLEMAN: Yes; I think that was the cause of the deformity.

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CHILDREN'S HOSPITAL HONORED

RECENTLY, at the annual meeting of its trustees and corporation, the Children's Hospital of Boston paid its respect to eleven staff members who had received outstanding medical awards during the year. The most notable of these was, of course, the Nobel Prize in Medicine, bestowed on Drs. John F. Enders, Thomas H. Weller and Frederick C. Robbins — an event already marked in these columns.* Dr. Enders was also the recipient, with Dr. Robert E. Gross, of the Lasker Award of the American Public Health Association. Others cited by the Hospital were Dr. James L. Gamble, who won the Moxon Medal of the Royal College of Physicians, London; Dr. Sidney Farber, who received the Judd Award of the Memorial Center and Sloan-Kettering Institute; Dr. Thomas H. Lanman, who was awarded the first William E. Ladd Gold Medal of the American Academy of Pediatrics; Dr. Edward B. D. Neuhauser, who was given the gold medal of the American Roentgen Ray Society; Drs. Carlyle G. Flake and Charles F. Ferguson, who were joint recipients of the gold medal of the Pan American Congress of Otorhinolaryngology and Broncho-Esophagology; and Ferdinand R. Harding, who won the Louis Schmidt Award of the Biological Photographic Association.

In the words of the president of the Hospital the honors attained are "possibly without parallel in the history of any hospital." Certainly, the joint accomplishment represented by the various awards is impressive. To the earlier prizes, some of them in purest gold, the Children's Hospital has added a tribute in no less welcome metal: a heartfelt expression of esteem from associates proud to labor alongside those whose achievements are an inspiration at home and abroad.

*Editorial. Return from Stockholm. *New Eng. J. Med.* **252**:112, 1955.

DR. FAULKNER CALLED TO M.I.T.

THE Massachusetts Institute of Technology and Dr. James M. Faulkner are equally to be congratulated on an appointment that will take effect next summer. At the end of the present academic year Dr. Faulkner will reactivate his clinical interests without abandoning his administrative experience by becoming medical director of the Institute, charged with the medical responsibility for its students and for its faculty and employees not otherwise cared for.

The new appointment brings to mind and serves to accentuate the good feeling that prevails in the diversified academic community of Greater Boston. The Henry K. Oliver chair of hygiene at Harvard left vacant by the retirement of Dr. Arlie V. Bock last year has been filled by Dr. Dana L. Farnsworth, until then medical director at the Institute, and Boston University School of Medicine is now surrendering its

dean as a distinguished replacement for Dr. Farnsworth. One is reminded of the game of stagecoach, except that there is a chair for everybody; no one is left out.

Nor need any alarm be felt about the future of Boston University School of Medicine. Not only has it had the wise leadership of Dr. Faulkner during more than seven years of striking progress, initiating something like a chain reaction, but it will have his continued service as professor of clinical medicine. A new dean will need only to carry on while formulating his own program.

During Dr. Faulkner's term of office grants in research have been increased from a total of $165,000 in 1947–1948 to a current total of $291,401, and teaching grants from $34,700 to $145,268. In the same period the faculty membership has increased from 266 to 413. Equally important are agreements reached with Boston City Hospital, the Boston and Providence Veterans Administration hospitals and the Lemuel Shattuck Hospital, greatly increasing the School's teaching and research facilities.

Dr. Faulkner, who graduated from Harvard College in 1920, after having served overseas in an engineer regiment, received his degree in medicine in 1924, also from Harvard. During World War II he served for five years in the Navy, retiring as a captain. A member of the American Society for Clinical Investigation, the American Clinical and Climatological Society, the Council on Medical Education and Hospitals of the American Medical Association and the editorial board of the *Journal of Medical Education,* he is also a vice-president of the American Academy of Arts and Sciences and a trustee of Phillips Exeter Academy. He was for several years a member of the editorial board of the *Journal* and now serves on the Committee on Publications.

INTERIM SESSION

The residents of rocky fastnesses are traditionally expected to repel invaders, and so it may have been at one time with the inhabitants of New England. The attitude has changed, however, in a more recent period; the population has softened, and when it comes to a matter of planning the interim session of the American Medical Association to be held in Boston this fall, the welcoming motions that have been made have lacked nothing in warmth and cordiality.

New England is mentioned particularly in this preliminary announcement because the pattern of the coming meeting will be somewhat different from that which has prevailed during the experimental sessions held in other parts of the country. Whereas single cities (and to some extent the states that contain them) have hitherto played host to the off-beat assembly in the short period of its existence, this year a geographically unique and historically independent aggregation of the original colonies will direct its resources to the fulfillment of the enterprise.

A delegate has accordingly been appointed from each of the medical societies of the 5 states that share with Massachusetts the New England heritage, and already, on January 20, these representatives have met with the local committee in the famous Blue Room of the Harvard Club of Boston to lay plans for what is expected to be, when the moment arrives, the Greatest Show on Earth.

The local committee, which will put into execution the plans and decisions of the larger group, transforming its visions into gracious realities, is composed of Dr. Frank P. Foster, chairman, 605 Commonwealth Avenue, Boston; Dr. Charles S. Davidson; Dr. Laurence B. Ellis; Dr. Richard Warren and Dr. Thomas A. Warthin. In emphasizing the dedication of the entire medical profession of New England to this gigantic act of hospitality, the committee urges that suggestions for scientific papers and exhibits for the meeting, which will be held from November 29 to December 2, be submitted to it from the whole 6-state area.

LANTERN-SLIDE PROJECT FOR CASE RECORDS

It is approximately a year since, with the aid of a grant from the United States Public Health Service, the Massachusetts General Hospital launched a program of supplying each week 35-mm. lantern slides of x-ray films, gross specimens and photomicrographs with the current Case Records published in the *New England Journal of Medicine.* These slides were sent to subscribers who use the Case Records as a teaching exercise at medical-society meetings, medical clubs, medical-school classes and similar groups. Approximately 100 groups asked for this service; they include subscribers in almost every state in the union and in 12 foreign countries. During the year about 300 lantern slides were sent to each group.

Although the actual cost is around $100 per year, each subscriber was asked to pay only $25, the remainder being carried by the United States Public Health Service grant. The editorial staff of the Case Records now believe that if the lantern slides are being used intelligently by an interested group, the organization should be willing to support the entire cost. They are therefore not asking for renewal of Government support, and, beginning March 1, 1955, the cost for this service will be $100 a year. Subscribers who are interested in receiving the slides may write to Dr. Benjamin Castleman at the Massachusetts General Hospital for an application form.

To Correspondents. — *The following papers have been received: — On Climacteric Disease. An Account of the two Medical Institutions in Louisville, Ky., by Viator. (We shall be glad to publish this communication, if the author will send us his name.) On Intense Cold as an Anaesthetic. An Address delivered before the South Middlesex Medical Society.*

Boston M. & S. J., *Feb. 8, 1855*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON PHARMACEUTICAL PROBLEMS

The Committee on Pharmaceutical Problems brings the following information to the attention of the fellows of the Society.

The *Principles of Medical Ethics* of the American Medical Association were amplified by vote of the House of Delegates in San Francisco on July 17, 1954, by the addition of four new sections to Chapter 1.

Section 8 is as follows:

> It is unethical for a physician to participate in the ownership of a drugstore in his medical practice area unless adequate drugstore facilities are otherwise unavailable. This inadequacy must be confirmed by his component medical society. The same principle applies to physicians who dispense drugs or appliances. In both instances, the practice is unethical if secrecy and coercion are employed or if financial interest is placed above the quality of medical care. On the other hand, sometimes it may be advisable and even necessary for physicians to provide certain appliances or remedies without profit which patients cannot procure from other sources.

This principle was confirmed by the delegates at the Miami meeting in December, 1954.

Many physicians are apparently still unaware that under Section 3, Chapter 577, of the *General Laws* of Massachusetts, approved June 7, 1954, an oral prescription for a harmful drug (any drug on which the manufacturer has placed the caution "federal law prohibits dispensing without prescription") must be confirmed by the delivery of a written prescription to the pharmacist within seven days. Any physician who violates this provision shall be punished by a fine of not more than $25 for each violation.

DEATHS

Balcom — Kenneth I. Balcom, M.D., of Worcester, died on January 2. He was in his seventy-second year.

Dr. Balcom received his degree from Harvard Medical School in 1910. He was a fellow of the American Medical Association.

He is survived by his widow.

Levinson — Leon Levinson, M.D., of Newton, died on January 9. He was in his thirty-sixth year.

Dr. Levinson received his degree from Tufts College Medical School in 1943. He was an assistant professor, Tufts College Medical School, a member of the staffs of the Boston City, Beth Israel, Faulkner and Massachusetts Women's hospitals and a fellow of the American Medical Association.

He is survived by his parents, widow, two sons and a brother.

Wilson — Stanley A. Wilson, M.D., of Salem, died on January 11. He was in his fifty-eighth year.

Dr. Wilson received his degree from the University of Vermont College of Medicine in 1920. He was a member of the staffs of the Essex County Sanatorium and the Salem, Addison Gilbert, Mary Alley and Cable Memorial hospitals, a fellow of the American College of Radiology and the American Medical Association and a member of the American Roentgen Ray Society and the New England Roentgen Ray Society.

He is survived by his widow and a son.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1954

RÉSUMÉ

Disease	Dec. 1954	Dec. 1953	Seven-Year Median
Chancroid	1	3	3
Chicken pox	1318	1184	1455
Diphtheria	5	3	10
Dog bite	667	736	654
Dysentery, bacillary	18	43	7
Encephalitis, infectious	4	0	2
German measles	119	77	77
Gonorrhea	204	192	186
Granuloma inguinale	1	0	0
Hepatitis, infectious	106	118	15†
Lymphogranuloma venereum	2	0	1
Malaria	0	0	1
Measles	6752	49	199
Meningitis, meningococcal	5	7	7
Meningitis, Pfeiffer bacillus	4	2	5
Meningitis, pneumococcal	1	3	3
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	10	6	5
Mumps	1526	1288	1267
Poliomyelitis	25	59	19
Salmonellosis	22	13	4
Scarlet fever	319*	371	387
Syphilis	123	198	180
Trichinosis	1	0	3
Tuberculosis, pulmonary	234	182	201
Tuberculosis, other forms	21	5	11
Typhoid fever	0	0	1
Undulant fever	1	0	1
Whooping cough	317	157	331

*Includes streptococcal sore throat.
†Five-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, scarlet fever and whooping cough.

Only 5 cases of diphtheria were reported during December. With this in mind, it is interesting that in 1923, the year in which the immunization program against this disease began to be pushed, 1102 cases were reported in December.

Diseases above the seven-year median were bacillary dysentery, German measles, infectious hepatitis, measles, mumps, poliomyelitis and salmonellosis.

Although the enteric diseases (bacillary dysentery, infectious hepatitis and salmonellosis) were above the seven-year median for December, an encouraging feature was that all three showed a decrease from the preceding month.

Repercussions from the unbelievably low levels for measles reached during the fall and early winter of 1953-1954 appear now to be approaching their zenith. During the month of December 6752 cases were reported — by far the highest for this month in the history of the State.

By a comfortable margin mumps, during December, also reached its high point for this month in the history of the State.

Geographic Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Boston, 2; Lawrence, 1; Natick, 1; Seekonk, 1; total, 5.

Dysentery, amebic: Pittsfield, 1.

Dysentery, bacillary: Boston, 9; Pittsfield, 1; Waltham, 1; Williamstown, 4; Wrentham, 3; total, 18.

Encephalitis, infectious: Mattapoisett, 1; New Bedford, 2; Winthrop, 1; total, 4.

Hepatitis, infectious: Beverly, 2; Boston, 9; Brockton, 5; Cambridge, 8; Chelsea Naval Hospital, 5; Chicopee, 1; East

Bridgewater, 1; Fall River, 15; Fitchburg, 3; Framingham, 1; Lawrence, 1; Lexington, 1; Lowell, 14; Lynn, 1; Manchester, 1; Marshfield, 1; Natick, 1; New Bedford, 1; North Adams, 2; Northboro, 2; Pittsfield, 1; Scituate, 1; Seekonk, 3; Shrewsbury, 1; Somerset, 2; Somerville, 2; Springfield, 4; Waltham, 4; Westminster, 1; Williamstown, 1; Worcester, 9; Wrentham, 2; total, 106.

Meningitis, meningococcal: Braintree, 1; Chelsea, 1; Easthampton, 1; Holyoke, 1; Watertown, 1; total, 5.

Meningitis, Pfeiffer bacillus: Cambridge, 1; Palmer, 1; Salem, 1; Worcester, 1; total, 4.

Meningitis, pneumococcal: Boston, 1.

Meningitis, mumps: Worcester, 1.

Meningitis, undetermined: Arlington, 2; Burlington, 1; Cambridge, 1; Lee, 1; Lowell, 1; Pittsfield, 1; Springfield, 1; Waltham, 1; Worcester, 1; total, 10.

Poliomyelitis: Ashland, 1; Boston, 2; Chicopee, 1; Duxbury, 1; Fall River, 1; Hudson, 1; Lynn, 4; Marshfield, 1; Newton, 2; North Adams, 1; North Reading, 1; Princeton, 1; Saugus, 1; Sudbury, 2; Watertown, 1; Wayland, 1; West Springfield, 1; Winchester, 1; Worcester, 1; total, 25.

Salmonellosis: Boston, 6; Brookline, 1; Cambridge, 1; Medford, 1; Newton, 1; Southampton, 4; Springfield, 1; Watertown, 2; Winchendon, 2; Worcester, 3; total, 22.

Trichinosis: Watertown, 1.

Undulant fever: North Attleboro, 1.

CORRESPONDENCE

MEDICAL-CARE PROGRAM

To the Editor: The editorial in the October 14 issue of the *Journal* called attention to the fact that the Blue Cross and Blue Shield plans realized that they were not meeting the legitimate requirements of the public and had made a welcome extension in their basic coverage by the development of a prolonged-illness certificate. The welcome extension was presumably made by these insurance plans on the recommendation of their official medical leadership, which is apparently pushing health insurance on a financial basis to cover expenses of hospitalization, surgery, some medical care and other high-cost procedures.

One wonders if the official medical leadership realizes what the laymen who, as consumers, are trying to organize health insurance for themselves desire. A few quotations from the statement of Nelson H. Cruikshank before the Committee of Interstate and Foreign Commerce (often spoken of as the Wolverton Committee) in January, 1954, might present briefly the laymen's point of view (Mr. Cruikshank is the director of social insurance activities for the American Federation of Labor):

> Resolution adopted by the 72nd Annual Convention of the American Federation of Labor.
>
> The delegates call upon the Congress of the United States to provide a nationwide system of national health insurance to assure that good medical care will be made available to all of the people of America.
>
> A constructive, progressive medical care program is one which seeks to improve and to maintain the health of those who are served by it, rather than merely to patch up and repair their disabilities after they have reached an advanced stage.
>
> The only really constructive and hopeful approach to that basic problem is one which seeks to preserve health, to prevent disease, and to check its progress at the earliest possible stage. It is upon this approach that the major emphasis of any national health program properly belongs. It is the only way in which the actual cost of medical care can be progressively improved.
>
> A constructive health program based upon the principle of prevention as well as cure, should encourage, prepay the costs of, and provide facilities for regular physical examinations and the earliest possible diagnosis and treatment of symptoms and ailments. It should make the services and facilities of all the various specialties as well as of general practitioners, working together, readily and conveniently available to the individual. It should provide for the continuing education and guidance of the individual in the use of the facilities available to him and in the proper care of his own health and that of his family. It should provide those who suffer from chronic conditions ready access to the kind of attention and advice they need in order to prevent their condition from growing worse, and, if possible, to improve it. All of these services and facilities should be closely integrated with those which are provided for the hospitalization, care and treatment of more advanced cases of illness and disability.

Although I have only mentioned the desires of one large group of our citizens, lists are available of many other large and small groups as well as many individuals and practicing physicians who support this philosophy.

Granted that the official medical leadership and the consumers of medical care are both striving to bring to all the American people the best of medical care, it is obvious that there is disagreement on the best method of procedure. Sufficient examples of successful insurance plans exist (for example, Health Insurance Plan of Greater New York, or H. I. P.), which provide the services that the consumers want to show that they are practical. Unfortunately, many of these plans are bitterly opposed by so-called organized medicine.

Would it not be well for official medical leadership of health-insurance plans to get in closer touch with the consumers of medical care and thus to see if the two philosophies might be molded into one, especially since successful plans that suit the consumer already exist and the officials of Blue Cross and Blue Shield realize that the plans are inadequate?

CHANNING FROTHINGHAM, M.D.
Boston

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Larvierte Eisenmangelkrankheit. By B. Jasiński and Dr. O. Roth, Medizinische Abteilung des Kantonsspitals Winterthur. 8°, cloth, 206 pp., with 33 illustrations. Basel: Benno Schwabe and Company, 1954. Geb.Fr.19.- (Distributed by Intercontinental Medical Book Corporation, New York.)

This comprehensive monograph deals with masked deficiency of iron in the blood and its relation to the anemias. A bibliography of over 4 pages is appended to the text. An index would have improved the book. The volume should be in all collections on the blood.

A Synopsis of Children's Diseases. By John Rendle-Short, M.A., M.B. (Cantab.), M.R.C.P., D.C.H., senior registrar, Department of Child Health, Welsh National School of Medicine. 12°, cloth, 608 pp. Bristol: John Wright and Sons, Limited, 1954. $7.00. (Distributed in America by Williams and Wilkins, Baltimore.)

This synopsis is fully detailed, and the material is well arranged in a systematic manner. The text is divided into two main parts: the healthy child and the sick child. The part on the sick child is arranged by classes of diseases and systems of the body. There are chapters on psychologic disorders, allergic diseases, inborn errors of metabolism and accidents in childhood. There are two appendixes on drug dosage and on normal values in clinical pathology. There is a comprehensive index, and the publishing is excellent. The book should prove valuable to the general practitioner and to the pediatrician.

Symposium On Protein Metabolism. Proceedings of the Nutrition Symposium held at the University of Toronto, Toronto, Ontario, Canada, October 30, 1953. By A. E. Axelrod and others. 8°, paper, 107 pp. New York: National Vitamin Foundation, Incorporated, 1954. $1.50. *(Nutrition Symposium Series,* No. 8.)

This collection of seven papers deals with the role of the vitamins in various aspects of protein metabolism and in treatment.

Essentials of Legal and Medical Competency. By Isadore Green, M.D., chief neuropsychiatrist, Jewish Memorial Hospital, Soldiers Home Hospital, associate neurologist, Beth Israel Hospital, and lecturer in neurology, Tufts College Medical School. 8°, paper, 70 pp. Boston: Medico-Historical Press, 1954.

This manual presents a summary of the basic laws concerning legal and medical competency and their adjudication in the courts of Massachusetts. It is interesting that a physician cannot withhold information on the ground that it is confidential.

A Primer of Pulmonary Function. By Harold Guyon Trimble, M.D.; and James Kieran, M.D. 8°, paper, 22 pp. Oakland, California: Printed through the co-operation of California Tuberculosis and Health Association, 1954.

This primer presents a summary of the basic pulmonary-function tests.

Physical Aspects of Betatron Therapy. By John S. Laughlin, associate professor of biophysics, Cornell University Medical College, Sloan-Kettering Division, and Department of Physics, Memorial Center for Cancer and Allied Diseases, New York City. 8°, cloth, 98 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $3.75. (Publication No. 196, *American Lecture Series.*)

This monograph deals with the use of high-energy x-ray and electron beams as a means of treatment. The author discusses especially the physics of the betatron machine. The text is divided into two sections on the x-ray beam and the electron beam. There is a bibliography of 94 references and a good index.

The Diagnosis and Treatment of the Infertile Female. By Fred A. Simmons, M.D., assistant surgeon, Massachusetts General Hospital, assistant surgeon, Free Hospital for Women, Brookline, Massachusetts, and instructor in gynecology, Harvard Medical School, Boston, Massachusetts. 8°, cloth, 83 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $2.50. (Publication No. 220, *American Lecture Series.*)

This gynecologic monograph by an authority on infertility is about evenly divided between diagnosis and treatment. There are chapters on treatment of the various female organs and one on the treatment of the patient that includes lists of books for the physician and for the patient or relatives. This is an important bibliography. There are short chapters on artificial insemination, adoption and the psychosomatic approach. A short general bibliography is appended to the text, and there is a good index.

Hormones in Health and Disease. Edited by Robert L. Craig, M.D. 8°, cloth, 346 pp., with illustrations. New York: Macmillan, 1954. $6.00. (A symposium presented at the twenty-fifth Graduate Fortnight of the New York Academy of Medicine, October 6 to 17, 1952.)

The twenty-fifth Graduate Fortnight of the New York Academy of Medicine was devoted to a symposium on hormones during which 23 authorities contributed papers on the various aspects of the subject. This third volume of the series should be in all medical libraries. Lists of references are appended to the papers and there is an index.

De abditis nonnullis ac mirandis morborum et sanationum causis. By Antonio Benivieni of Florence. Translated by Charles Singer. With a biographic appreciation by Esmond R. Long. 8°, cloth, 217 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1954. $6.75.

Benivieni, recognized as one of the founders of pathological anatomy, presents in his classic text a series of case histories. First published by the Giunta press at Florence in 1507 it is a source book in any edition; it has now been reprinted in facsimile with an opposing translation in English. The publishing is excellent, and the book is recommended for all medical libraries and to all pathologists.

The Cyclopedia of Medicine, Surgery, Specialties. Editor-in-chief, George Morris Piersol, M.D., professor of medicine and director of the center for research and instruction in physical medicine, Graduate School of Medicine, and professor of physical medicine, University of Pennsylvania School of Medicine; assistant editor, Edward L. Bortz, M.D., associate professor of medicine, Graduate School of Medicine, University of Pennsylvania. 1954 revision of the 14 volumes. 4°, looseleaf pages, with illustrations. Philadelphia: F. A. Davis Company, 1954. (Subscription basis.)

In this revision for 1954 the contributors offer much new and valuable material. There are new sections on chronic arthritis and vectorcardiography. Endocrinology is presented by a new group of authors, and new material is included. Several of the important articles on cardiology have been revised.

Kinderorthopädie. By Dr. med. habil., Dr. rer. nat. and Dr. phil. Rupprecht Bernbeck, lecturer in orthopedics, Universität München. With a foreword by Prof. Dr. Dr. h.c. Georg Hohmann, München. 8°, cloth, 232 pp., with 174 illustrations. Stuttgart: Georg Thieme, 1954. DM 39.—($9.30). (Distributed in America by Intercontinental Medical Book Corporation, New York.)

This special book on the orthopedics of children has been written for the general practitioner, the school physician, pediatrician, children's surgeon and obstetric nurse. The text is systematically arranged and is divided into two parts, general and special. The general part discusses the anatomy of the skeletal system and the pathology, diagnosis and treatment in general. The special deals with the parts of the body taken in anatomic order from the lower to the upper extremities. There are chapters on congenital systemic diseases, acquired skeletal conditions (rickets, osteomyelitis, arthritis, tuberculosis and so forth) and traumatic conditions. There is a bibliography and a good index. The publishing is excellent.

Der Herzkatheterismus bei angeborenen und erworbenen Herzfehlern. By Prof. Dr. Otto Bayer, chief physician, l.med.Klinik, Düsseldorf; Dr. Franz Loogen, assistant, l.med.Klinik, Düsseldorf; and Dr. Hans Helmut Wolter, assistant, l.med.Klinik, Düsseldorf. With a foreword by Prof. Dr. Erich Boden, director, l.med.Klinik, Düsseldorf. 8°, cloth, 191 pp., with 131 illustrations. Stuttgart: Georg Thieme, 1954. $8.60. (Distributed in America by Intercontinental Medical Book Corporation, New York.)

The authors in this monograph discuss catheterization of the heart in congenital and acquired defects. The text is divided into two parts, general and special. The first deals with the principles, technic, complications and method of the procedure. The special part deals in detail with various congenital and acquired defects. The literature is surveyed, and there is a bibliography of over 12½ pages. There is a good index, and the publishing is excellent. This valuable monograph should be in all collections on the heart.

Parkinsonism and Its Treatment. Edited by Lewis J. Doshay, M.D., M.A., Ph.D. 12°, cloth, 152 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1954. $3.00.

This small book, the work of nine authorities in their special fields, was originally published in part in the *American Practitioner and Digest of Treatment* (November, 1953). The anatomy, etiology, pathology, symptomatology and various forms of treatment are dealt with. Lists of references are appended to the chapters, and there is an extensive index. The text presents the latest information on the disease. The book is recommended to all medical libraries and to all physicians interested in the subject.

NOTICES

FRAMINGHAM GENERAL HOSPITAL LECTURE

Dr. Clifford Derick will deliver a lecture on the topic "Cirrhosis of the Liver" on February 15, at 9 p.m., at the Framingham General Hospital.

SOUTH END MEDICAL CLUB

A meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on February 15 at noon. Dr. David Landau will speak on the subject "The Early Recognition and Treatment of the Problem Drinker with Particular Reference to Antabuse Therapy." All physicians are invited.

FOUNDATION OF THE AMERICAN SOCIETY OF PLASTIC AND RECONSTRUCTIVE SURGERY

The Foundation of the American Society of Plastic and Reconstructive Surgery announces a scholarship contest for 1955 and awards for contestants in two classifications.

Contestants for the junior classification must be residents in training or plastic surgeons with less than five years' practice, residents of the American continent, British Dominions or Western Europe. Essays must be about 5000 words in length, not previously published, in English on the results of clinical or experimental original research in plastic and reconstructive surgery and submitted in quadruplicate before July 1. A separate envelope must include the author's name, address and institutional affiliation, with details of professional training and percentage of practice in plastic surgery. Character references from two leading plastic surgeons in the applicant's country must be sent to the Award Committee at the time the essays are submitted in a separate envelope.

The awards for the junior classification consist of $1000 in cash and a three months' scholarship for the first prize and $750 in cash and a three months' scholarship for the second prize.

Contestants in the senior classification — the prize consisting of a silver plaque or certificate of honorable mention — must have been in active practice of plastic and reconstructive surgery for more than five years. The stipulations for the junior classification apply also to the senior classification.

Manuscripts must be mailed to the Award Committee, The Foundation of the American Society of Plastic and Reconstructive Surgery, 30 Central Park South, New York 19, New York.

EARL D. OSBORNE FELLOWSHIP

The American Academy of Dermatology and Syphilology announces the Earl D. Osborne Fellowship in Dermal Pathology, providing the opportunity for study and training in dermal pathology to a postgraduate student who has completed satisfactorily one year's or, preferably, two years' training in dermatology.

The stipend is $4000, divided into quarterly payments during the year. The training will be received at the Armed Forces Institute of Pathology, Washington, D. C. Another year of graduate training will be required for the board examinations in dermatology; it may be taken before or after the year at the Institute.

Further information may be obtained from Dr. Hamilton Montgomery, Committee on Pathology, American Academy of Dermatology and Syphilology, 200 First Street Southwest, Rochester, Minnesota.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY–APRIL. Postgraduate Medical Institute. Page 451, issue of September 9.
FEBRUARY–MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
FEBRUARY 7. New England Cardiovascular Society. Page 157, issue of January 27.
FEBRUARY 7–9. McIntyre–Saranac Conference. Page 410, issue of September 2.
FEBRUARY 7–23. Consultation Clinics for Crippled Children in Massachusetts. Page 155, issue of January 27.
FEBRUARY 7–MAY 9. Seminar in Psychiatry and Neurology. Page 452, issue of September 9.
FEBRUARY 8. Harvard Medical Society. Page 157, issue of January 27.
FEBRUARY 9. Videclinic. Page 156, issue of January 27.
FEBRUARY 11 and 12. International College of Surgeons. Page 157, issue of January 27.
FEBRUARY 11–25. Pan-American Academy of General Practice. Page 496, issue of September 16.
FEBRUARY 11–MARCH 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.
FEBRUARY 15. Tufts Medical Alumni Association Lecture. Page 157, issue of January 27.
FEBRUARY 15. New England Deaconess Hospital Lectures. Page 993, issue of December 9.
FEBRUARY 15. South End Medical Club. Notice above.
FEBRUARY 15. Framingham General Hospital Lecture. Page 201.
FEBRUARY 26 and 27. Mid-Winter Radiologic Conference. Page 1076, issue of December 23.
FEBRUARY 28–MARCH 1. International College of Surgeons, Southwestern Division Regional Meeeting. Page 157, issue of January 27.
FEBRUARY 28–MARCH 2. American Orthopsychiatric Association. Page 994, issue of December 9.
MARCH 5–MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.
MARCH 7–12. Course in Care of Atomic Casualties. Page 285, issue of August 12.
MARCH 20–23. Aero Medical Association. Page 157, issue of January 27.
MARCH 23–26. International Academy of Proctology. Page 876, issue of November 18.
APRIL 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.
APRIL 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.
MAY 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
MAY 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 10

THURSDAY, FEBRUARY 10
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Thoracic Conference. Pulmonary Vascular Anomaly. Dr. Alexander Nadas. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, FEBRUARY 11
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, FEBRUARY 12
*8:00 a.m. Gynecological Grand Rounds. 6th-floor conference room. Carney Hospital, 2100 Dorchester Avenue, Dorchester.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

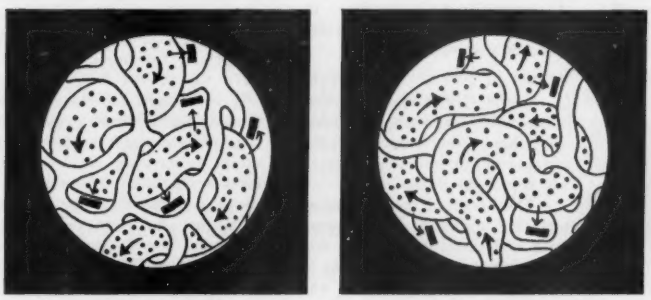
(Concluded on page xxxv)

MICTINE*—THE NEW ORAL DIURETIC

Searle MICTINE Provides Effective Oral, Non-Mercurial Diuresis

The result of many years of research, Mictine, brand of aminometramide, supplies a long-felt need for an improved oral diuretic. Mictine, 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione, is not a mercurial, xanthine or sulfonamide.

Effectiveness: Every method for measuring the diuretic effect in man now available, including precise human bioassay studies, without exception demonstrated that Mictine is an effective oral diuretic, and these studies show that approximately 70 per cent of *unselected* edematous patients treated with Mictine by mouth respond with a satisfactory diuresis.



Mictine is believed to act by the selective inhibition of the reabsorption of sodium ions. Thus, the resulting diuresis is characterized by increased quantities of sodium ions and water.

Well-Tolerated: There are no known contraindications to Mictine, even in the presence of hepatic or renal damage, and there is no risk of acidosis. On high dosage, Mictine causes some side effects in some patients but on three tablets daily these side effects (anorexia and nausea, rarely vomiting, diarrhea or headache) are minimal or absent.

Indications: Mictine is useful primarily in the *maintenance* of an edema-free state and in the *initial and continuing* control of patients in mild congestive failure. Mictine may be used also for *initial and continuing* diuresis in *more severe* congestive states, particularly when mercurial diuretics are contraindicated.

Administration: The usual dosage for the average patient is one to four tablets daily with meals, in divided doses on an interrupted schedule. An interrupted dosage schedule may be accomplished by giving the drug on alternate days or for three consecutive days and then omitting it for four days.

For severe congestive states the dosage is four to six tablets daily with meals, in divided doses on interrupted schedules similar to those already mentioned.

Supplied: Uncoated tablets of 200 mg.

**Trademark of G. D. Searle & Co.*

SEARLE

DAVIS TECHNIC
FOR
VAGINAL TRICHOMONIASIS

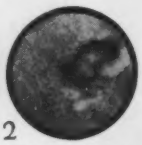
EXPLODES TRICHOMONADS

WITHIN 15 SECONDS

VAGISEC, a new agent for the treatment of vaginal trichomoniasis, was originated as "Carlendacide" by Dr. Carl Henry Davis, well-known gynecologist and C. G. Grand, research physiologist.

Vagisec's triple action kills trichomonads within 15 seconds of contact. Its unique synergism "captures" calcium, removes lipid materials, and literally explodes the trichomonad — all within 15 seconds!

1 *Microphotograph (phase contrast microscope) of a Trichomonas vaginalis*



2 *Trichomonad "exploded" within 15 seconds of contact with* VAGISEC *liquid as used in douche*

Debris and mucus hide trichomonads. Trichomonads do not exist in vaginal secretion alone. They are vigorously motile and burrow deeply into the surface of the vaginal mucosa, covered by cellular debris and mucus. Vagisec penetrates this protection by lowering surface tension. It penetrates into the folds of the vaginal mucosa.

Vagisec attacks three ways. The chelating agent in Vagisec attaches itself to the calcium of the calcium proteinate, weakening the surface of the trichomonad. The wetting agent in Vagisec removes waxes and lipid materials from its surface, allowing the detergent in Vagisec to move into the cell, breaking up its structure by denaturing the protein. Then water moves in and blows up the trichomonad.

No other agent or combination of agents kills the trichomonad in this specific fashion, or with the speed of Vagisec.

Result of intensive research. Davis and Grand made studies[1] of commonly used trichomonacides. They showed that most antiseptics coagulated albuminous material, which protects trichomonads.

They realized that a satisfactory trichomonacide had to penetrate and dissolve mucinous material. It had to be non-irritating to the already inflamed mucosa and lethal to the trichomonad on brief contact.

Based on these concepts, an exhaustive study[2] of all available new trichomonacidal agents resulted in the development and patenting of "Carlendacide." Clinically tested, "Carlendacide" proved to be a remarkably fast-acting, effective treatment for vaginal trichomoniasis. Dr. Davis recommends a combination of office treatment and home treatment, the Davis technic.

Office treatment. The vagina is exposed with a speculum. The walls of the vagina are wiped dry with cotton sponges and then thoroughly washed with a 1:250 dilution of Vagisec. (Thorough washing takes about three minutes.) The vagina is then dried with cotton sponges. The patient can leave the office without a tampon, or messy discharge or staining.

A minimum of six office treatments are recommended: three the first week, two the second, and one the third week.

Home treatment. Both VAGISEC liquid and VAGISEC jelly should be prescribed for home treatment. Have the patient insert VAGISEC jelly each night and douche with VAGISEC liquid (1 teaspoon to a quart of warm water) each morning except on days she receives treatment at the office. This treatment should continue through two menstrual periods. Four weeks after treatment, the douche should be omitted at least three days and the patient re-examined.

Afterwards, the patient should continue douching with Vagisec at least two or three times each week as a precaution against re-infection.

Summary. Vagisec kills trichomonads in 15 seconds. Failure due to lack of penetration is eliminated. Vagisec is non-toxic and leaves no discoloration or messy discharge. The Davis technic is a triple attack of Vagisec office treatment, home treatment, and Vagisec jelly. Vagisec has been clinically tested and proved as a remarkably fast-acting, effective treatment for vaginal trichomoniasis.

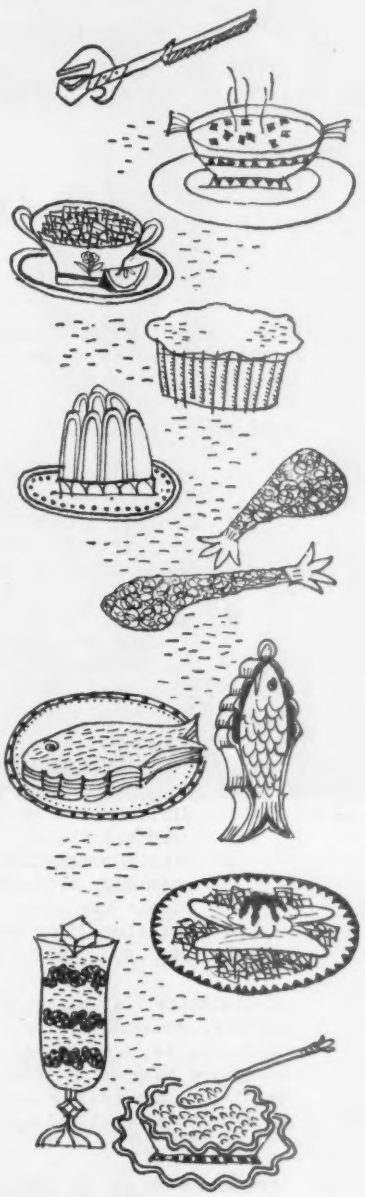
References: 1. Davis, C. H.: J.A.M.A. 92:306, 1929. 2. Davis, C. H.: Am. J. Obst. & Gynec. 68:559 (Aug.) 1954.

JULIUS SCHMID, INC., *gynecological division* 423 West 55th Street, New York 19, N. Y.

VAGISEC IS THE TRADE-MARK OF JULIUS SCHMID, INC., FOR PRODUCTS TO BE USED IN THE CONTROL OF VAGINAL TRICHOMONIASIS

The "quick'n easy" of Low-Residue Diets...

Starting with a can opener as key to this diet, your patient has a wide choice of unseasoned strained or chopped foods. And these diet "do's" can guide him toward tempting, tasty dishes.



Vary the texture for taste appeal—

Consommé can be served hot with crisp croutons, or cold and jellied in shimmering peaks. Puréed vegetables folded into a well-beaten egg can be baked to a puff, or molded in gelatin. Finely chopped beef moistened with broth spreads for a sandwich—mixed with bread crumbs, it shapes into patties. Eggs can be soft or hard cooked by simmering—or scrambled in a double boiler.

Serve prettily for eye appeal—

Chopped meat can be shaped like a chop—minced chicken like a drumstick—before baking. And flaked fish in lemon gelatin looks true to nature when your patient uses a mold.

White potatoes mashed with a little broth whip up creamy and light with cottage cheese. And mashed sweet potatoes made smooth with orange juice can be baked in the orange shells.

Banana split salad may tempt your patient. For the "greens," suggest lime gelatin shredded with a fork. Add a ball of cottage cheese to the split banana and top with puréed apricots.

Rice cooked in pineapple juice, water, and sugar makes a golden dessert. And for a gay parfait—alternate layers of farina pudding with puréed plums. Then put a sparkling cube of clear jelly on top.

Of course, you'll want to tell your patient just which foods you want him to have. And these ideas can help him enjoy them in many ways that are quick, easy, and appetizing.

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Beer—America's Beverage of Moderation

pH—4.3, 104 calories/8 oz. glass (Average of American beers)

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l-Glutavite

A cerebral tonic for the geriatric patient

Dear Doctor:

A new concept in the treatment of cerebral decompensation in the elderly was recently presented at the New England Postgraduate Assembly. By the use of the unique metabolic stimulant, l-Glutavite, you can demonstrate in your own practice that a majority of typical geriatric complaints can be alleviated. Among many recent clinical observations, certain are especially pertinent:

1. After glutamate therapy, "17 out of the 27 patients were improved.... Of the 17 who improved, 16 improved in action...patients...on occupational therapy do their jobs better...showed more interest in their work." (Himwich, H.E., et al.: Paper presented at American Psychiatric Association meeting, St. Louis, May, 1954.)

2. "Niacin produces often striking therapeutic effects in...'total cerebral decompensation'....A trial with nicotinic acid...is always indicated, particularly in elderly patients." (Lehmann, H.: Proceedings, 27th Annual Conference, Milbank Memorial Fund, New York, Paul Hoeber, Inc., 1952, p. 587.)

Besides these clinical trials, these facts emerge from basic studies:

1. Glutamic acid participates specifically in the nutrition of cerebral tissue.
2. Orally, monosodium levo-glutamate raises blood levels of glutamic acid much more effectively than the free acid itself.
3. Niacin has notable vasodilator effects on cerebral circulation.
4. Thiamine, riboflavin, ascorbic acid and their associated minerals are important in cerebral cellular oxidations.

l-Glutavite* is indicated in the following geriatric states: weakness and fatigue, anorexia, vertigo, insomnia, depression, anxiety, and apathy. l-Glutavite is palatable and taken in vegetable or tomato juice, or sprinkled on prepared foods, stimulates the appetite. 3 to 5 packets daily constitute adequate dosage. We urge you to put this new biochemotherapeutic concept to a practical trial.

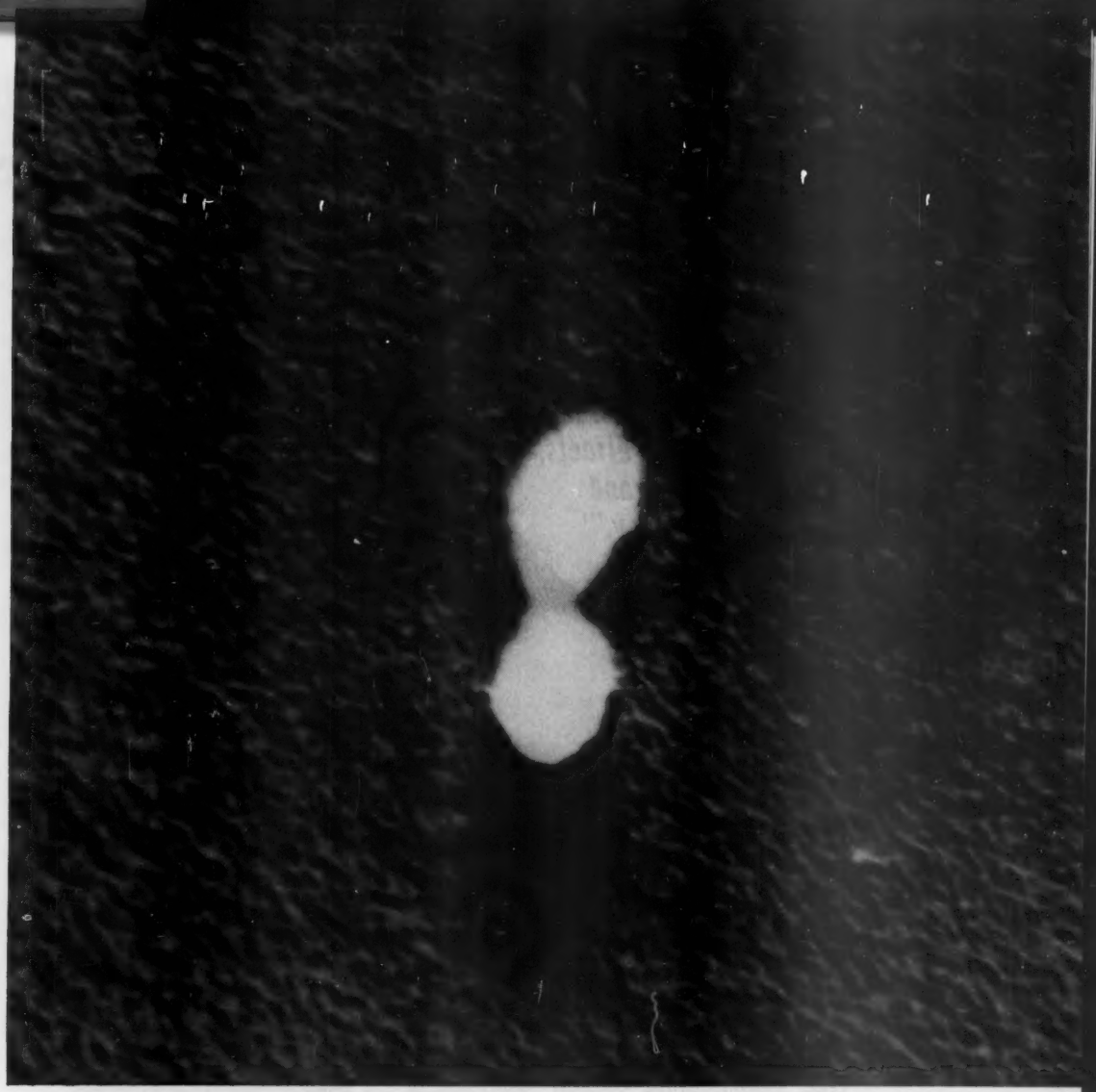
Sincerely,

Francis L. Colpoys M.D.

Medical Director

*Formula (per packet)

Monosodium levo-glutamate	3.48 Gm.
Niacin	45.0 mg.
Thiamine Mononitrate	0.6 mg.
Riboflavin	0.8 mg.
Ascorbic Acid	30.0 mg.
Ferrous Sulfate	11.0 mg.
Dicalcium Phosphate	910.0 mg.



ELECTRON PHOTOMICROGRAPH

Streptococcus faecalis 40,000 X

Streptococcus faecalis is a Gram-positive organism commonly involved in a variety of pathologic conditions, including

urinary tract infections • subacute bacterial endocarditis • peritonitis.

It is another of the more than 30 organisms susceptible to

PANMYCIN*

100 mg. and 250 mg. capsules

*250 mg./tsp. oral suspension (***PANMYCIN** *Readimixed)*

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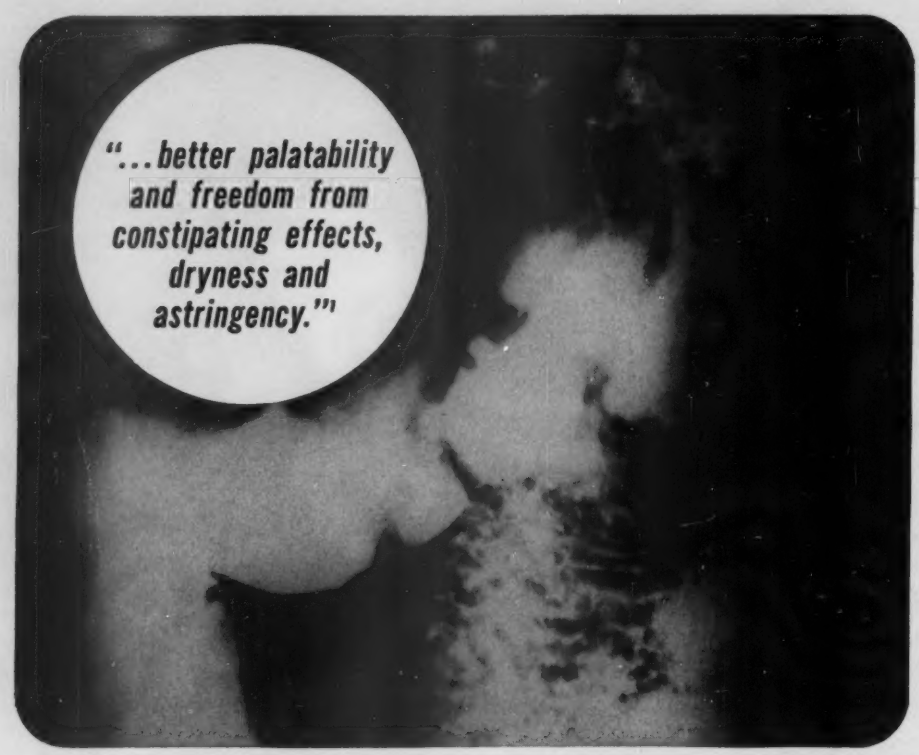

Morrison, in treating a large series of patients with Maalox-Rorer, describes this better-tolerated preparation as "... a palatable, antacid, demulcent, nonconstipating colloidal suspension of magnesium and aluminum hydroxides, useful for the relief of hyperacidity."

This clinician concludes: "Magnesium aluminum hydroxide gel is more palatable than aluminum hydroxide gel and better suited to the prolonged administration required for the antacid therapy of peptic ulcer and hyperchlorhydria."[1]

A well-balanced suspension, notable for its smooth texture and pleasant flavor, Maalox has gained remarkable patient acceptance.

Supplied: in 355 cc. (12 fluid ounce) bottles. In tablet form, bottles of 100. Each tablet equivalent to 1 fluidram of the suspension.

Samples sent promptly on request.

maalox®
controls hyperacidity

1. Morrison, Samuel: Magnesium aluminum hydroxide gel in the antacid therapy of peptic ulcer, Am. J. of Gastroenterology 22:309 (Oct.) 1954.

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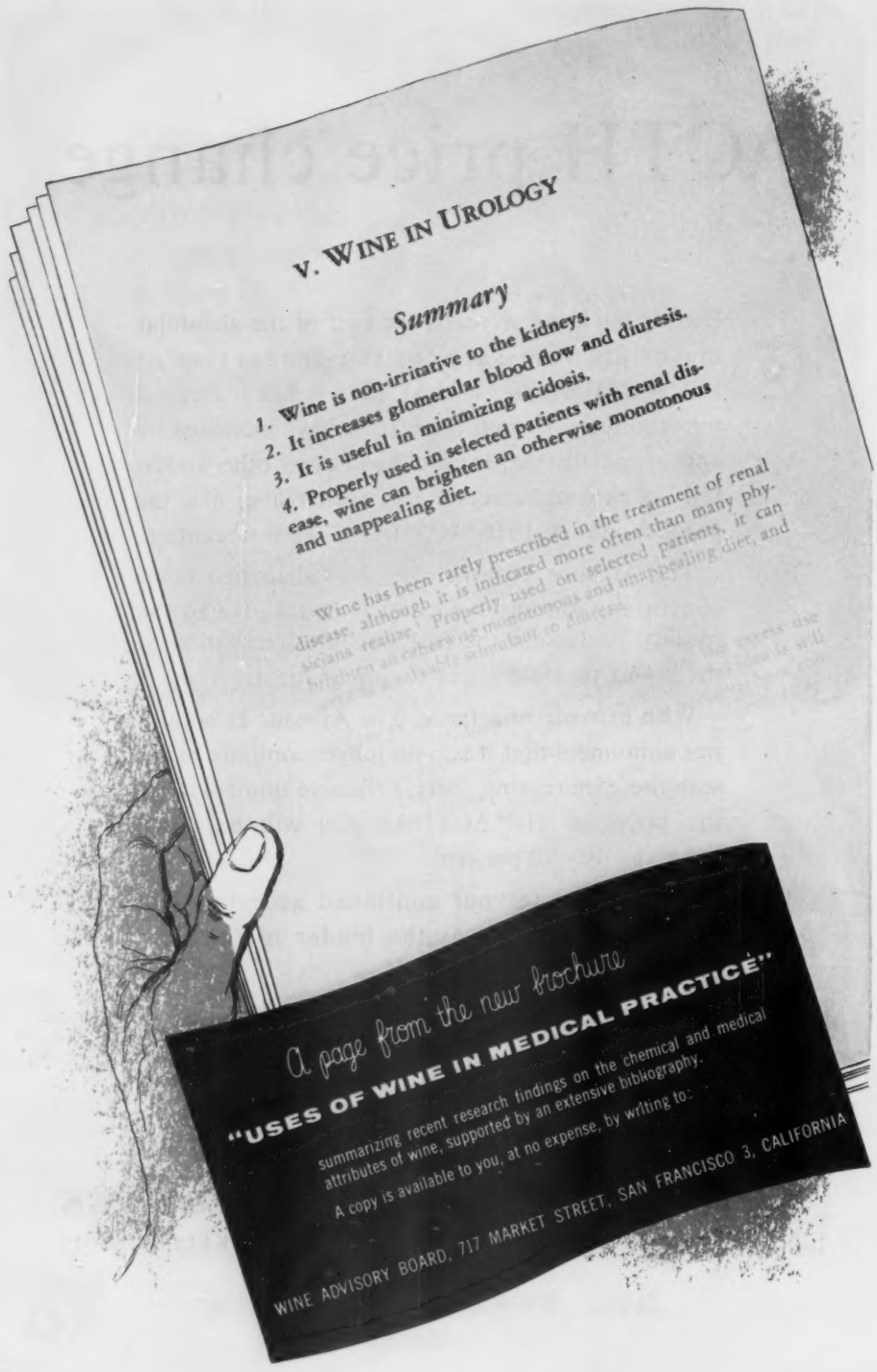
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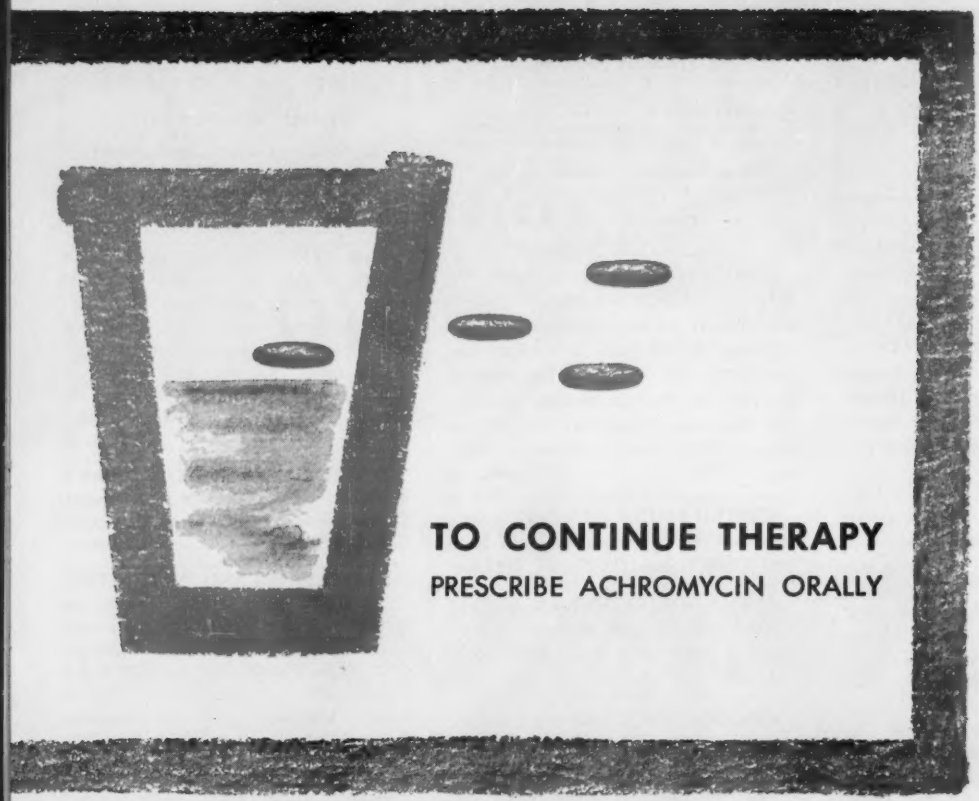

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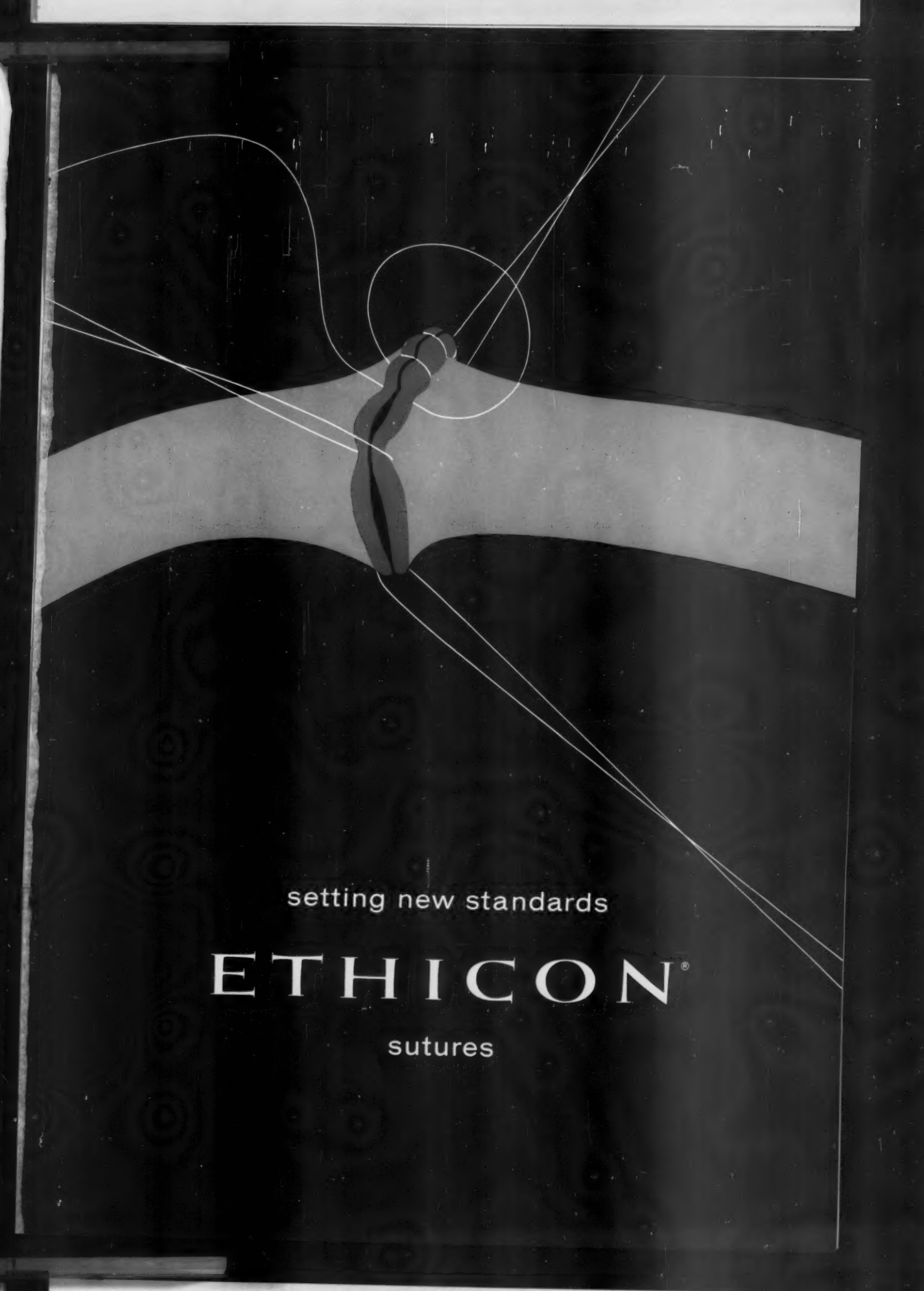
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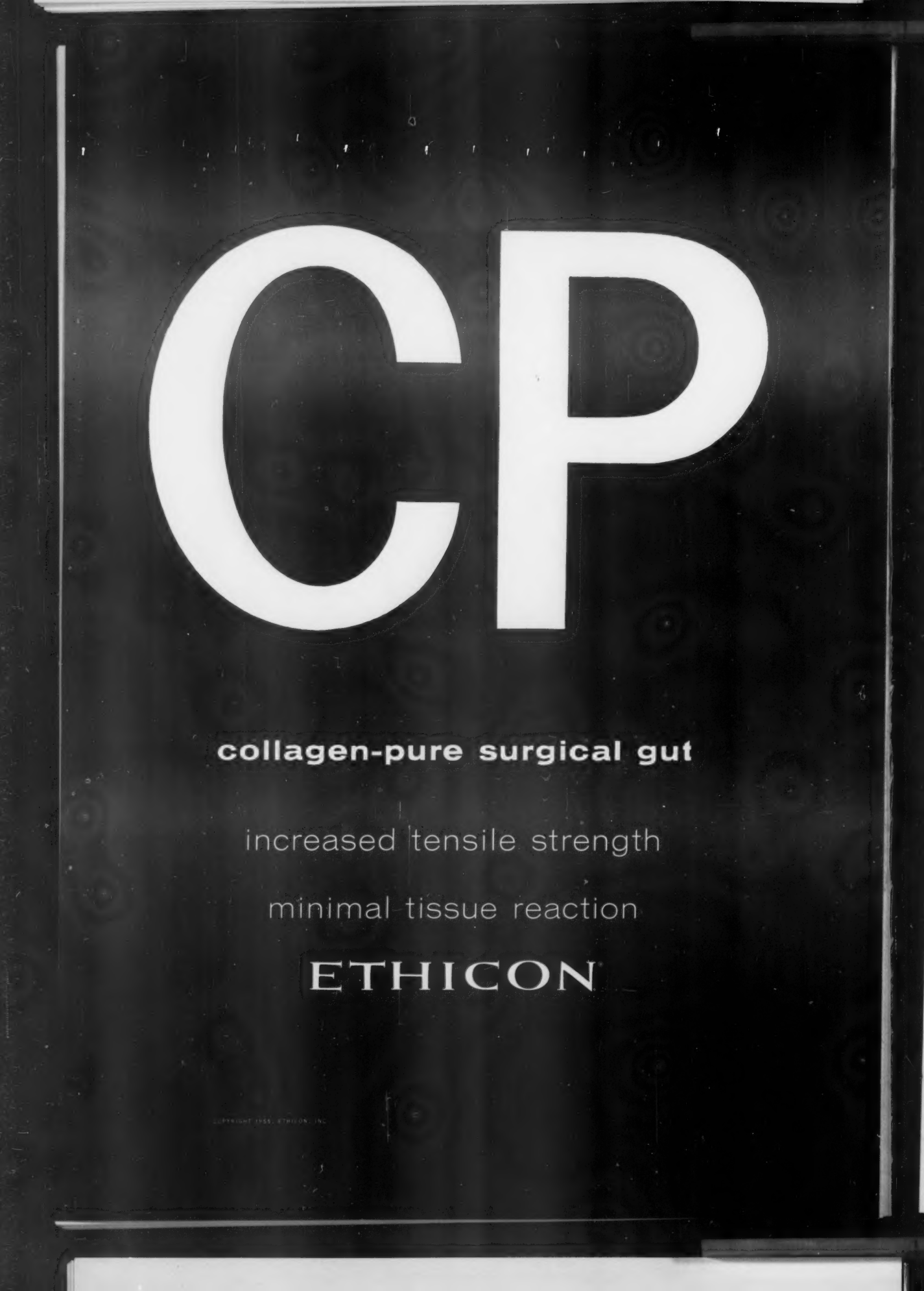
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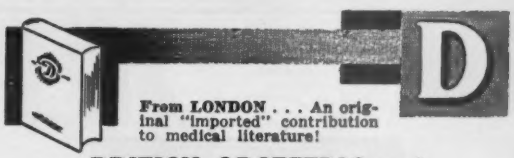

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Index to Advertisers

	PAGE
The Armour Laboratories	xxiii
Baldpate, Inc.	xxxii
Bilhuber-Knoll Corp.	xxix
Boston Medical Laboratory	xxviii
The Children's Memorial Hospital	xxx
Ciba Pharmaceutical Products, Inc.	Back Cover
David Memorial Nursing Home	xxxii
Davies Rose & Company, Ltd.	xxxiii
F. A. Davis Co.	xxix
Electroencephalographic Laboratory, Inc.	xxviii
Endo Products, Inc.	xxxi
Ethicon, Inc.	After xxviii
Fine Chemicals	vi, vii
Glenside, Inc.	xxxii
Gray Pharmaceutical Co., Inc.	xx
Hanover House, Inc.	xxxii
Hoffmann-La Roche, Inc.	After viii
Lederle Laboratories	xxvi, xxvii
Thos. Leeming & Co., Inc.	xxxv
Eli Lilly and Company	xvi
Medical Clearing Bureau, Inc.	xxxii
The Wm. S. Merrell Company	xv
Parke, Davis and Company	ii, iii
Perkins School	xxxii
Pfizer Laboratories (Div. of Chas. Pfizer & Co., Inc.)	xii, xxxiv
Ring Sanatorium	xxxii
A. H. Robins Company, Inc.	xiv
J. B. Roerig Co.	iv
William H. Rorer, Inc.	xxii
Royal Victoria Hospital	xxix
W. B. Saunders Company	Front Cover
Julius Schmid, Inc.	xviii
G. D. Searle and Company	xvii
Sharp & Dohme (Division of Merck & Co., Inc.)	ix, xi, xxx
Smith, Kline & French Laboratories	v
E. R. Squibb & Sons (Division of Mathieson Chemical Corporation)	x
Storrow House (Massachusetts General Hospital)	xxviii
United States Brewers Foundation, Inc.	xix
The Upjohn Co.	xiii, xxi, xxv
Washingtonian Hospital	xxxii
J. S. Waterman & Sons	xxx
Wine Advisory Board	xxiv
Wiswall Sanatorium	xxxii
Woodside Cottages, Inc.	xxxii

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(Concluded from page 202)

*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, FEBRUARY 14
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Therapeutic Conference. Dr. McCombs. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Pharmacology of Local Anesthetics. Dr. Burnap. Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–8:00 p.m. Pathology Conference. Dr. MacMahon and Staff. Stearns Auditorium, New England Center Hospital.

TUESDAY, FEBRUARY 15
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.
12:00 m. South End Medical Club. Boston Tuberculosis Association, 554 Columbus Avenue, Boston.
*12:00 m.–1:00 p.m. Pediatric Combined Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic, New England Deaconess Hospital.
*4:00 p.m. Tufts Medical Alumni Association Lecture. Medicine, Men and Money. Dr. John F. Conlin. Tufts College Medical School.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:45 p.m. New England Deaconess Hospital Lectures. Electrolyte and Fluid Balance. Dr. Elmer E. Hinton. Joslin Amphitheater, New England Deaconess Hospital.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
7:00 p.m. Adrenal Cortical Steroids and the Autonomic Nervous System. Dr. Rachmiel Levine. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
9:00 p.m. Framingham General Hospital Lecture. Framingham General Hospital.

WEDNESDAY, FEBRUARY 16
*8:00 a.m. Combined Rounds. Massachusetts General Hospital.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m. Boston State Hospital. Psychiatry Seminar. Therapy of Paranoid-Schizophrenic Patients. Dr. Alfred Stanton. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

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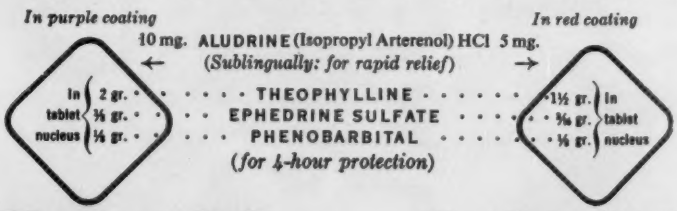

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